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14. ABSTRACT
The near-infrared spectroscopy (NIRS) research project is a three-part project over three years, intended to validate the accuracy and reliability of a specific NIRS sensor (INVOS, Somanetics Inc, Troy, MI) in diagnosing acute compartment syndrome in injured combat soldiers. Part 1 is a planned series of two 6-month observational studies. Patients will receive continuous NIRS and vital sign monitoring throughout their standard course of care, first at Landstuhl Regional Medical Center and then at frontline combat support hospitals in Afghanistan. This Phase 1 of Part 1 has been initiated and is nearing completion. The Phase 2 observational study is currently under review by the Medical Research and Material Command (MRMC) Institutional Review Board (IRB) review. Part 2 involves animal studies aimed at addressing issues raised in clinical testing and furthering the understanding of NIRS response to compartment syndrome. This phase of study will occur in Period 2 under Institutional Animal Care and Use Committee (IACUC) approved protocols, which have also been approved by the Animal Care and Use Review Office (ACURO). The final part of this project will be the translation of the current technology into a proven format, approved by the Food and Drug Administration (FDA). This requires the data collected in parts 1 and 2, as well as ongoing regulatory steps and iterative maturation of the interpretation of NIRS data in the diagnosis of acute compartment syndrome (ACS).

15. SUBJECT TERMS
Near-Infrared Spectroscopy; Acute Compartment Syndrome; Combat Casualty; Diagnosis; Tissue Oxygen Saturation

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INTRODUCTION:

The near-infrared spectroscopy (NIRS) research project is a three-part project taking place over three years, intended to validate the accuracy and reliability of a specific NIRS sensor (INVOS, Somanetics Inc, Troy, MI) in diagnosing acute compartment syndrome in injured combat soldiers. Part 1, which is currently ongoing, is comprised of two 6-month observational studies ("Phase 1" and "Phase 2"), which will enroll 135 patients each. Patients will receive continuous NIRS and vital sign monitoring throughout their standard course of care, first at Landstuhl Regional Medical Center (LRMC; Phase 1) and then at frontline combat support hospitals (CSH) in Afghanistan (Phase 2). Phase 1 is nearing completion.

The Phase 2 observational study was severely delayed, secondary to the Medical Research and Material Command (MRMC) Institutional Review Board (IRB) approval process, which ultimately required transitioning this protocol from a waived-consent protocol, which was approvable under the "Common Rule" for medical research (45 CFR 46), to a Food and Drug Administration (FDA) abbreviated Investigational Device Exemption (IDE) regulated clinical study, which required consent. On 6 Oct 2010, the MRMC IRB provided final approval of the Phase 2 protocol with one stipulation. While these obstacles have delayed the starting date of Phase 2, they will ultimately lead to a landmark study, as it will be the first FDA IDE study to ever be performed in combat.

Part 2 involves animal studies aimed at addressing issues raised in clinical testing and furthering the understanding of NIRS responsiveness to compartment syndrome. This phase of study will occur in Period 2 under Institutional Animal Care and Use Committee (IACUC) approved protocols (University of Georgia IACUC – Protocol #: A2010 1-012), which have since been approved by the Animal Care and Use Review Office (ACURO; APPENDIX 1).

The final part of this project (Tasks 4-6) will be the translation of the current technology into an FDA-approvable format. The current FDA-approved indication for the Somanetics INVOS 5100C (FDA 510-K 080769 (5/14/2008); APPENDIX 2), which is the device we are testing, is:

> "The noninvasive INVOS 5100C is intended for use as an adjunct trend monitor of regional hemoglobin oxygen saturation of blood in the brain or in other tissue beneath the sensor. It is intended for use in any individual at risk for reduced-flow or no-flow ischemic states. The prospective clinical value of data from the INVOS System has not been demonstrated in disease states. The INVOS System should not be used as the sole basis for diagnosis or therapy."

The only distinction between this indication and a subsequent indication, which we seek to develop, submit and defend through the clinical and animal research completed/initiated in support of this 3-year grant, is that the device is currently indicated as a physiological monitor. The future indication would be as a diagnostic device.

This requires the data collected in parts 1 and 2, as well as ongoing regulatory steps and iterative maturation of the diagnostic algorithm. Our experience in Phase 1, on top of the pre-grant experience of Dr. Shuler (co-investigator; APPENDIX 3), has confirmed that the physical technology contained in the INVOS 5100C is sufficient to obtain a reliable signal that accurately indicates the oxygen saturation in the tissues underlying the INVOS sensors for the purpose of acquiring data that will then be interpreted to diagnose the presence or absence of, or provide a risk stratification for, Acute Compartment Syndrome (ACS). Thus, there is no need for significant physical modification of the device. Innovations to the technology will not come in the physical form, but in the interpretation of data. Due to FDA regulation, we will now be including data from the Phase 2 observational study in the planned FDA application. In June 2010, we submitted a request to revise the United States Army Medical Research Acquisition Activity (USAMRAA) statement of work (SOW) to exclude this study's data from Task 4; however, this exclusion is no longer necessary

BODY:

The primary goal of work conducted in Period 1 was to initiate the project, hire and resource the research team, complete Phase 1 enrollment, begin Phase 2, and obtain IACUC/ACURO protocol approval for the animal studies that will occur at the University of Georgia in 1st quarter, Period 2.

To date, we have completed 100% enrollment for Phase 1. The completed control cohort (Cohort 1) has resulted in a better understanding of NIRS values in a healthy, uninjured physiologic state. Findings from this cohort were presented at the 2010 Society of Military Orthopedic Surgeons (SOMOS) annual meeting in Vail, CO (13-17 December 2010), and will be presented at the American Academy of Orthopedic Surgeons (AAOS) in San Diego, CA (15-19 February 2011) (Appendix 4). We are also in the process of compiling these results into a manuscript for peer-reviewed publication. Selected results from the analysis of Phase 1 Cohort 1 are included in Appendix 5.

The data analysis for Cohorts 2 and 3 is on-going. We have only recently completed enrollment for these cohorts, which had been delayed for several unforeseeable reasons. The primary reportable research findings of the Phase 1 study come solely from the results of Cohort 1. This cohort is not replicated in the Phase 2 study. Cohorts 2 and 3 in Phase 1 allow for final validation of the physical technology, in that we were able to obtain reliable NIRS values from all injured extremities in all enrolled patients. But these patients are 48+ hours removed from the time of injury and those with, or at-risk for, ACS had already undergone fasciotomy prior to arrival at LRMC. The primary value of Cohorts 2 and 3, which was recognized in the development of this protocol, was to validate the research protocol itself. Phase 1 allowed associate investigators to mature and perfect the methodology of this study and become fully familiarized with the idiosyncrasies of the device. For example, we learned that the NIRS sensors cannot be placed directly over a Wound Vacuum Assisted Closure (V.A.C.) device, as the black sponge in this dressing absorbs all light. This will have no bearing on the clinical efficacy of the NIRS device as a means for diagnosing ACS, as the V.A.C. sponges were placed AFTER fasciotomy, which is AFTER the question of whether ACS is present or not has been definitely answered. The importance of the validation of the protocol itself cannot be over-stated, as the success of Phase 2 is only guaranteed through the delivery of a "fool-proof" protocol for patient enrollment, data acquisition and recording. In this respect, Cohorts 2 and 3 have served their purposes well, and we expect limited reportable data to be generated from these two specific cohorts. Research in a combat zone is exponentially more challenging than in the controlled environment of a civilian medical center. Prior experience has proven universally that protocols which are not first trialed in the civilian sector are doomed to failure in the combat zone. There has been a substantial learning curve for this protocol, including overcoming network communication issues, data synchronization, and designing the most ergonomic way to maintain the wires coming from the sensors. All issues which, if forced to be learned by deployed researchers in austere environments, would have doomed our project as well. As

USAMRAA continues to encourage in-theater grant-supported research, it must understand that pre-deployment validation of the protocol is an essential first step to success.

Our Phase 2 Protocol was submitted to the Joint Combat Casualty Research Team (JC2RT) team on 25 Mar 2010, and subsequently passed on to the Army Institute of Surgical Research (AISR) on 7 June 2010. There, it passed formal scientific review and was forwarded to the USAMRMC IRB for their final approval on 8 July 2010. On 11 August 2010 the MRMC IRB reviewed the Phase 2 protocol in committee. We responded, to MRMC's satisfaction, to all revisions requested in the minutes of this meeting by 8 Sep 2010. Following this, our Phase 2 protocol stalled, pending an FDA pre-IDE determination ordered by MRMC. The results of this determination were that the Phase 2 study must be conducted under abbreviated IDE FDA requirements. Specifically, this requires informed consent, which was not required under the standard of the Common Rule for human research.

On-site evaluation was conducted to confirm that the consent requirement would not doom the protocol to failure. Due to the transition in combat operations, specifically the improved use of mine resistant ambush protected (MRAP) vehicles, the types of injuries have changed and the ability to obtain consent in-theater does not appear to be a critical detriment, but one that will definitely slow the enrollment process. Thus, the protocol was revised to conform to the required format. Consequently, the Phase 2 study will become the first FDA IDE trial to ever be performed in a combat setting.

In addition to slowing enrollment, the revised protocol also required the addition of two more sites to the study (Camp Dwyer and the Kandahar Role III hospitals), which will be supported by the JC2RT. Due to the changing mission in Afghanistan, currently Bagram only sees about 10% of the acute trauma cases reaching Level III hospitals. The details of the protocol revisions and their impact on this study were openly discussed in a series of three teleconferences on 9 September through 29 September 2010, in which I indicated, in my opinion and that of the JC2RT members at Bagram, that the Phase 2 study was doable with consent, but that it would delay our completion by 1-2 quarters. This was satisfactory to all. On 6 Oct 2010, the MRMC IRB met ad hoc, and approved the current version of the protocol with one stipulated change. Specifically, an FDA compliant medical monitoring plan must be added. LTC Shoemaker has since written a medical monitoring plan that is acceptable to the MRMC IRB and will serve as the template for future FDA IDE abbreviated studies in-theater.

Since then, the new commander of the Kandahar Role III hospital has stated that he did not feel informed consent can or should be obtained from traumatized soldiers. To this end, consent for medical procedures is not obtained from patients at this facility. This resulted in a series of events that has ultimately shut down all prospective clinical research using medical devices (four studies) occurring in-theater. Based on the actions of the MRMC, FDA oversight has been or will be sought for all four of these studies. In turn, each of these studies, which were approvable under the Common Rule with waived consent, were immediately disapproved for initiation or continued enrollment. This ultimately resulted in a presentation to the CENTCOM Surgeon on

or about 25 Nov 2010. LTC Rob Eckart (current chief of the JC2RT) presented on behalf of all PIs impacted by MRMC's actions. This presentation did two important things. First, it informed the senior medical command that this issue existed. Second, it brought universal agreement that a solution must be achieved that allows for continued prospective medical device research that is deemed nonsignificant risk to occur in the combat theater. The result of this meeting was the promotion of this issue to the office of the Surgeon General for all three military services. This is where the issue lies currently. It is planned that the FDA will review this issue and a request is pending from the Department of Defense (DoD), specifically seeking an exemption for waived consent for FDA IDE trials occurring in the combat zone, similar to a current exemption which exists for specific emergency medical procedures tested in the civilian environment. Until a final solution has been reached for this problem, the Phase 2 study, like all prospective medical device studies in theater, will be placed on hold. This request is included in APPENDIX 6.

Over the last 7 months, we have arduously sought to avoid, and then mitigate, the string of delays associated with the approval of this protocol, but nonetheless, they occurred in sequence beyond our control. Throughout, we have been in frequent conversation with MRMC to track the progress of this situation. We have kept our grant office representative (GOR) at USAMRAA fully briefed on the status of this delay.

The following tasks from our statement of work were addressed over the last year:

TASK 1. Human Use Study Phase 1

1a. Create and submit SAMMC Human Use IRB Protocol Application, Principal investigators complete CITI training. – *Completed.*

The Phase 1 protocol, entitled "The use of near-infrared spectro scopy in the diagnosis of acute compartment syndrome in injured soldiers" *was declared as* no greater than minimal risk *by the SAMMC Human Use IRB, and was approved on 27 August 2009 for the period of one year (control number C.2009.201). This study is comprised of a six-month observational studies that has recently reached full enrollment. Details of study progress are described below.*

All study investigators (Brett Freedman, Michael Shuler, Debra Lackie, Lesa Owens, and Arthur Ethington) completed CITI certification training during Quarter 1 of Period 1, in preparation for study start-up.

On 29 June 2010, the Phase 1 protocol was approved under continuing review for the period of one additional year. Future continuing review reports will be submitted in June 2011 if necessary.

1b. Obtain clearance and impact statements from LRMC commander, LRMC DCCS, LRMC Chief of Division of Surgery, LRMC Chief of Trauma Program, LRMC Research Review Committee, ERMC MEDCOM, CIRO, USAMRMC (2nd Level DoD IRB) – *Completed*

Clearance and impact statements were obtained from all necessary personnel in Quarter 1, Period 1.

1c. Hire 2 research coordinators (LRMC site) and 1 Project Manager (J&M Shuler site) prior to starting Phase 1. – *Completed*

Two research coordinators (Debra Lackie and Lesa Owens) were hired at the LRMC site during the 1st Quarter of Period 1. These coordinators serve as primary data collectors and enrollment personnel in the Phase 1 and 2 studies in Part 1, and maintain the study database. Throughout all periods of the grant, they ensure that regulatory reporting requirements for the IRB and FDA are being upheld. The research coordinators directly interface with the J&M Shuler site.

A project manager was hired at the J&M Shuler site during the 1st Quarter of Period 1. This position involves clinical study design, design and maintenance of study databases, as well as data management and coordination of statistical analyses. The project manager interfaces on a regular basis with the research coordinators at the LRMC site.

All study personnel participated in introductory briefings and were trained in preparation of Phase 1 initiation. Office furniture, computers, and software were also successfully purchased and installed.

1d. Initialize Patient Enrollment (months 0-3). – *Completed.*

Because of minor delays with the hiring of research coordinators at the LRMC site, as well as technological problems with the existing ICU monitors at LRMC, patient enrollment for Phase 1 was delayed by one quarter and began during the 2nd Quarter of Period 1. Nevertheless, patient enrollment for Phase 1 was successfully initiated and has recently been completed. Phase 1 enrollment of 135 subjects (45 in each of 3 cohorts (1 – controls; 2 – critical controls; 3 – lower extremity injured) was completed on 23 NOV 2010. Unexpected delays occurred which deferred completion of Phase 1, nevertheless, we were able to complete Phase 1 enrollment during the 1st Quarter of Period 2, which is <2 quarters delayed from our SOW, with no impact on the start dates for the Phase 2 clinical trial or the animal studies.

1e. Conduct Phase 1 Prospective Observational Study (months 0-9) – *Completed*

We finished behind schedule on this task, due to the reasons addressed in previous quarterly reports. Examples of problems we have had to overcome:

- *Delayed initiation date to 2 Feb 2010, because the Philips C70 Intellivue ICU monitors, which the LRMC medical maintenance personnel confirmed compatible with the Somanetics Vital Sync device were indeed compatible, but only if LRMC had purchased a 2nd data port. The funding (outside of DR 080018 funds), authorization and actual labor to complete this install took 1.5 months.*
- *Late April 2010 - Volcanic ash delayed air-evacuation flights in and out of Afghanistan and Germany for 2 weeks. Many patients following this event were re-routed around LRMC. This also delayed our re-supply shipment of INVOS leads an additional week. Another delay for volcanic ash occurred in mid-May.*
- *BAMC IRB halted the study for two weeks due to three reported adverse events (AE). These AEs were mild skin irritation, not an allergic reaction, but the response seen especially in pale skin people (like the 3 subjects with the AE) when you leave a band-aid on for a long time. The BAMC IRB formally reviewed this AE report and the allowed us to re-open the study.*
- *Phase 1 was a consent-required protocol from its initiation. This posed a significant challenge and greatly slowed the pace of enrollment, as we completed Cohort 1 (healthy controls) and enrolled subjects for Cohort 2 and 3. In fact, the requirement for consent is much more impactful on the Phase 1 enrollment than it will be on Phase 2. One of the reasons we started this research project was to address the over-use of a prophylactic procedure, namely fasciotomies. Another prophylactic procedure that is even more rampant is elective intubation. A high percentage of severely injured trauma patients, who present awake and alert to the trauma bay are intubated in-theater, after their initial evaluation (typically at their first operative visit), and remain intubated through transport to LRMC and then onto CONUS. While we have had the investigators and investigational devices, and have seen an abundance of eligible patients, few have been consentable.*
- *July-September 2010 - Increased casualty flow. These has been the most lethal and injurious months of conflict in Afghanistan. While higher numbers of patients meeting Cohort 2 and 3 inclusion criteria present to LRMC, they stay shorter periods of time. Thus, the window to consent and obtain sufficient data is further reduced. The opposite scenario consists of patients who are eligible and consentable for Cohort 3, but who are "too" awake and alert and too mobile to be able to participate in this study. The leads interfere with physical therapy and out-of-bed activities. This interference is not a clinically significant issue for the future, when the INVOS device becomes the standard of care for diagnosing ACS, as patients capable of out of bed activities are by definition not at risk of ACS.*

These delays were largely unexpected and unavoidable.

1f. Analyze Data, Provider Feedback and Amend Phase 2 Methodology as needed – *Ongoing*

Data Analysis: *We have successfully analyzed data from Phase 1 Cohort 1 patients and are in the process of compiling the findings into a manuscript for peer-reviewed publication. Research objectives addressed in the Phase 1 Cohort 1 analysis included:*

1. Assessment of the validity of NIRS values of the contralateral leg as an internal control
2. Assessment of the validity of NIRS values of the upper extremity as an internal control, when an uninjured lower extremity is not available
3. Evaluation of the reliability of NIRS measurements across days of monitoring
4. Descriptive statistics regarding the characteristics of NIRS values over time
5. Investigation of the effect of leg hair and shaving on NIRS values

Selected results from these analyses are included in Appendix 5.

Provider Feedback: *Modification of existing NIRS device was discussed with co-investigators as well as representatives from Somanetics during our investigator site visit during the 1st Quarter of Period 1. Changes were implemented to improve ease of use with the device, including pre-bundling of wires ("horse-tail") to avoid entanglement and/or safety concerns. A voluntary 3 item questionnaire was part of the data collection tool for Phase 1, however no provider volunteered to complete this section. The interaction between providers and the INVOS equipment has been minimal. This is to our credit as a research team, as it was a stated intent of our Phase 1 protocol that enrollment of the patient into our study would not interfere with usual care of the patient. Instead, "provider feedback" has come from the anecdotal experience and recorded issues which have been worked through prospectively between the associate investigators and Somanetics. Based on our experience with Phase 1 and that of Michael Shuler's previous work from Grady Memorial Hospital, we have concluded that there is no need for physical modification of the underlying technology. All innovation will be in the interpretation of NIRS data collected, which will transform this device from a physiological monitor to a diagnostic device.*

Amendment of Phase 2 methodology: *Based on data collected in Phase 1, the following changes were made to Phase 2 methodology:*

1. Monitoring of the volar and deltoid compartments as upper extremity internal controls, based on findings from Cohort 1 data

2. Creation of a protocol for syncing multiple NIRS devices prior to data collection downrange, given the lack of availability of the VitalSync device

3. Improvements to data collection tools that will be used downrange, including a streamlined case report form that will include only data that must *be collected downrange, which will then be supplemented by data abstraction occurring at LRMC.*

1g. Present/Publish Results of Phase 1 – *Ongoing*

Data from Cohort 1 of Phase 1 will be presented at the 2011 American Academy of Orthopaedic Surgeons.[1] This same abstract was presented at the 2010 Society of Military Orthopaedic Surgeons (SOMOS).[2] A copy of this abstract can be found in Appendix 4; the SOMOS poster is included in Appendix 7. We notified the PAO (Public Affairs Office) and OPSEC for their clearance. We are currently working on the manuscript draft of this abstract.

TASK 2. Human Use Study Phase 2

2a. Create and Submit Human Use IRB Protocol Application – *Completed*

As noted previously, we submitted our Phase 2 protocol and responded to reviewer comments in a timely fashion. We are awaiting final approval to allow initiation of this study. Our goal was to begin Phase 2 enrollment by Sep 2010. Once approved, we will begin enrollment immediately. In the time we have been delayed, we have worked on training-the-trainer techniques to ensure that on-site PIs are ready to initiate this protocol in a consistent fashion. We have also networked to include 2 additional combat medical treatment facilities that will allow us to more closely adhere to our original SOW timelines for this study.

2b. Obtain clearance and impact statements – *Completed*

All necessary clearance and impact statements have been obtained, except final IRB approval. This is contingent on the Surgeon General and FDA final solution to the issue of waived informed consent for combat trauma studies involving minimal risk.

2c. Recruit lead investigator for OEF and OIF CSH (rotates q6mo) - *Completed*

Dr. Keith Jackson was our first on-site PI for Phase 2 and spent the months of September and October 2010 at Bagram, assisting in the study set-up, recruiting Kandahar and Camp Dwyer as additional testing sites, as well as educating the JC2RT staff on the protocol. Debra Lackie and Lesa Owens (LRMC Research Coordinators) will continue the data collection on the Phase 2 enrollees once they return to Germany.

We have recruited a replacement for Keith Jackson at Bagram (John McGee, PhD (Maj)), as well as on-site PIs for Camp Dwyer (Lawrence Harrington, PhD (Col) and Kandahar (Brett Carner, DPM (Maj). Once the Phase 2 protocol is finally approved, we will be ready to start at all three locations.

2d. Conduct Phase 2 Prospective Observational Study – *To be completed*

This is the task that has been most affected by the prolonged MRMC IRB approval process and will continue to be affected by the requirement for consent. This task was scheduled to start in the 4th quarter of Period 1. Based on the approval time for the Phase 1 protocol through the San Antonio Military Medical Center (SAMMC) IRB, which took <6 weeks from the time of submission to full approval, we were completely on course until May 2010. This time is lost, but we will continue to move forward. Dr. Dwayne Taliaferro was present for at least two of the conference calls between myself and the MRMC IRB. He acknowledged an understanding of the predicament, and that it would delay our progress with this task. At this point, I suspect we will fall 1-2 quarters behind in our completion of the Phase 2 study. The overall project was designed to be compartmentalized, to minimize the impact that a delay in any part of the project will have one the others. This foresight based on a decade of military medicine experience means that, as parts become delayed, the project is not significantly delayed overall.

In preparation for the final ad hoc MRMC IRB committee meeting (10/6/10), I was asked to justify how the study can succeed with the requirement of informed consent, and I provided the following response:

> In response to the initial telcon between myself, Ms. Kline and LTC Shoemaker on Friday 24 September 2010, I immediately contacted CPT Keith Jackson who is currently deployed with the JC2RT at Bagram specifically to support the initiation of the Phase 2 protocol and asked him if it would be feasible based on current casualty mix to complete enrollment under the new requirement of informed consent. I asked subjectively and quantitatively. His response, which was echoed by his colleagues on the current JC2RT team was YES. They believed it would slow the pace of enrollment, but that given the evolution in the patterns of injuries seen in OEF since the deployment of MRAP vehicles, more and more wounded warriors are presenting in a state that is consentable. The protection afforded by the current generation of up-armored vehicles negates the primary (overpressure) and secondary (fragmentation) injury mechanism of IED blast. This is consistent with my anecdotal experience as the spine surgeon at LRMC, where 3 of the 4 patients we operated on last week for burst fractures, had severe lower extremity injuries, but they were closed or Grade 1 or 2 open fractures, more consistent with the type of injuries that occur in civilian high energy trauma. All three were not intubated during the course of their trauma bay work-up, and were consentable for surgical/invasive procedures performed in-theater.
>
> Quantitatively, based on a pull of the JTTR database from 12-19 Sep 2010, there were almost 600 acute medical evaluations across OEF, of which 4 patients reached Bagram within 12 hours of injury, in a consentable state (2 Cohort 1, 1 Cohort 2A, 1 Cohort 2C). The majority of acute trauma evaluations at Level III combat support hospitals occurred at Kandahar, followed by Dwyer, with Bagram coming in third.

> This data pull and the on the ground experience of the current JC2RT, not only lends support to the feasibility of moving forward with this study under a consent required protocol, but also highlights the fact that this protocol will most likely require expansion to Kandahar and possibly Dwyer, where more acutely injured soldiers meeting the eligibility requirements for our study are being seen. We have already made a site visit to Kandahar (KAF) and are in the process of securing the support necessary to expand to this site next. The JC2RT is already present at KAF and would be able to support this protocol at this location. Further, there is a realistic chance, that another orthopaedic volunteer may follow CPT Jackson, when his deployment ends. He would be the on-site PI for the KAF site. The next orthopaedic surgeon rotating to Bagram is Maj Shaka Walker from LRMC. He is familiar with the NIRS project and several of his patients have participated in the Phase 1 study at LRMC. He has already agreed to be champion for this project at Bagram when he deploys this fall. (30 SEP 2010 – Memo to the MRMC IRB)

The current JC2RT members believed that at least 12-15 consentable, eligible patients would present to KAF, Dwyer and/or Bagram every week. However, based on the position of the Kandahar commander, effective informed consent is not an option at his facility and this is the standard that is being applied across Afghanistan Level III hospitals. As stated, this issue is at the level of the Surgeon General and the FDA, and we expect a final determination soon.

****The most recent update is that, on Thursday 9 December 2010, an FDA committee took the request for exemption status for DoD sponsored research in a combat zone under consideration. No response has been returned as of the date of this report.*

We must add a word of caution to any prediction on start and completion dates for in-theater clinical research. One of the hardest and most consistent lessons learned one year into this ambitious three-year project, which constitutes, to the best of our knowledge, the first in-theater USAMRAA and now FDA-regulated research project, has been the unexpected hurdles, which have posed significant challenges to the on-time completion of our tasks. While the challenges have been numerous, we have negotiated them all, but at a pace not driven by our team, rather by the situation and/or administrative body creating the challenge.

TASK 3. Animal Use Study

3a. Create and Submit UGA IACUC Protocol Application – *Completed*

Dr. Steve Budsberg, principle investigator for the animal use study, and his team at the University of Georgia (UGA), together with our research team, have finalized the animal use protocol to be conducted during the 1st Quarter of Period 2. The protocol has been approved by IACUC and ACURO. This study is progressing on time as outlined in the initial statement of work.

3b. Obtain approval from UGA IACUC and USAMRMC ACURO – *Completed*

The project title "Near Infra-Red Spectroscopy to Reduce Prophylactic Fasciotomies for and Missed Cases of Acute Compartment Syndrome in Soldiers Injured in OEF/OIF" *(Protocol #A2010-1-012) was approved on 14 April 2010 by the IACUC at UGA. A copy of IACUC approval is included in Appendix 8. ACURO approval was received on 29 OCT 2010.*

3c. Initiate animal studies outlined under Aim 2. *– To be completed*

We will be set to initiate animal studies at the University of Georgia in the initial part of 1st quarter of Period 2, in accordance with our statement of work.

TASK 4. Reduction to Practice and FDA Approval Process

4a. Finalize product development relationships: - *Completed*

Over the course of Period 1, the LRMC team has forged successful relationships with the product developers at Somanetics and the J&M Shuler site. These contacts continue to be involved in several aspects of the research project, from planning to trouble-shooting. They have been responsive to product development and regular correspondences are ongoing.

4b. Begin reduction to practice process. Current embodiment is not ideal. Reduce pad size, improve pad adhesion, and add key alarm algorithms. *– Ongoing*

We have come to understand that the physical device as it exists is sufficient for our tasks. No significant physical modifications to the underlying technology will be needed, other than simple things like bundling the wires to better organize them. The adhesive has been sufficient in our experience. Likewise, using the pediatric sensors, which have the same sensor array, but in a smaller overall adhesive pad size, has not been an issue. Innovation is not needed in data collection capabilities of the Somanetics product, but rather in data interpretation with respect to this new indication (ACS diagnosis). No changes have been made thus far to the algorithms, however as we complete Phase 1 data collection we will start the process of analyzing the best way to interpret NIRS values as they relate to ACS. Data interpretation innovation will include modeling several algorithms for decision making, based on physical parameters currently collected by the Somanetics INVOS 5100C device and other data points collected in the Phase 1 protocol. The data from Phase 2 will further this understanding and modeling, as this phase of study will occur in the time period where clinical questions about ACS are most likely. This study will also answer military specific questions, like feasibility, which have no bearing on a planned FDA application.

4c.Produce final prototype for use in completion of Phase 1, all of Phase 2 and the investigational clinical study to be supported by a future grant. *– Completed*

No significant modifications to the current technological aspects are expected/planned. However, user interface improvements are underway. These changes are minor, and include: bundling wires for safety and ease of use, improved labels on the device and sensors to identify compartments, and a single connection port for all four cables (rather than four separate ports).

4d Respond to provider feedback re: functionality and industrial design - *Ongoing*

"Provider feedback" is ongoing. Implemented changes include the pre-bundling of lead wires. Changes planned for the future include the development of a single connection port for the wires, which now plug into 4 separate ports. No other significant provider feedback items have been submitted to date.

TASK 5. Coordination between study sites

5a. Bi-annual collaborators meeting – *Ongoing*

Given the technological complexity and geographic challenges of this project, constant collaboration is essential to the success of this project. Collaborators meetings have included the PI from each study site, expert consultants hired for the grant, representatives from Somanetics, and/or research coordinators/project managers, depending on the current stage of the project. The first collaborators meeting took place in December 2009 in Athens, Georgia at the J&M Shuler site, where discussion was based around upcoming studies, and the possibilities for improvement of the device. In July 2010, our second collaborators meeting was held at the LRMC site, and focused on improvement of the study database and streamlining of data collection processes, in preparation for the Phase 2 study. The most recent collaborators meeting occurred in November 2010 in Athens, Georgia, where statistical analysis of the data from Cohort 1 was finalized and the final presentation for the meetings in December and February was created. Additionally, we finalized the data collection tool for Phase 2, based on lessons learned in Phase 1. We also concluded that the minor improvements to the embodiment of the device listed in 4c above would be sufficient to represent a mature version of the INVOS 5100C for use as an ACS diagnostic device.

5b. Conduct weekly VTC (Telcon) for LRMC/J+M Shuler, and OIF/OEF during Phase 2 – *Ongoing*

Currently, teleconferences occur at least once a week, with additional calls scheduled as needed, between the LRMC and J&M Shuler sites. The agendas for these calls are driven by current progress and/or issues. Meetings with OIF/OEF will begin with the initiation of Phase 2.

5c. Rapid interpretation of weakness in the design and function of sequential NIRS pad prototypes and NIRS monitoring algorithms. *– Completed.*

As the data collection process proceeds, we have found that no modifications to the NIRS pads or monitoring algorithm are required. As noted previously, minor changes are under discussion regarding changes to sensor wires and connection ports.

5d. Coordinate response to FDA requests for information during approval process – *Ongoing*

This task is ongoing, depending on the stage of the project. With regards to Phase 2, the PI has worked with Ms. Andrea Kline at MRMC and LTC Shoemaker at USAMMDA to revise the protocol in accordance with FDA requirements for consent waived protocols.

5e. Ensure mandatory reporting to SAMMC, ISR & USAMRMC is maintained (quarterly) *– Ongoing*

We have continued to stay current with mandatory reporting procedures. On 29 June 2010, we received approval for continuation and notice of successful continuing review by the BAMC IRB for our Phase 1 protocol. Mandatory reporting will continue to be maintained with the Phase 2 study.

Task 6. Future Research Endeavors

6a. Create NIRS-based clinical guidelines based on results of Aim 1-3 (months 30-36) - *To be completed*

6b. Complete and submit a prospective clinical investigational study IRB application to validate NIRS-based clinical practice guidelines (Future Project) – *To be completed*

6c. Analyze data, publish/present, revolutionize diagnosis and treatment of ACS – *To be completed*

KEY RESEARCH ACCOMPLISHMENTS

1. Validated the contralateral leg as an internal control for patients with unilateral lower extremity injuries. This is useful due to high between-patient variability of NIRS values.

2. Described correlations between NIRS values of the lower extremity and those of various compartments of the upper extremity, which will be essential for patients with bilateral injuries.

3. Demonstrated reliability of NIRS values across multiple days of monitoring, important as many patients will be monitored for multiple days after injury.

4. Observed no significant differences between NIRS values collected prior to shaving (leg hair present) versus those collected post-shave (leg hair absent).

5. Demonstrated a moderate positive correlation between melanin values and NIRS values among subjects of White ethnicity

6. Product improvement of the current NIRS device via pre-bundling of wires prior to shipment, for convenience and safety, was a good temporary fix. In the future, it will be ideal to have the wires come pre-assembled such that they feed into a single data port connector, rather than the current embodiment, which has 4 separate connectors, which can come loose and take time to install.

7. INVOS NIRS sensors cannot detect tissue oxygen saturations under a Wound V.A.C. dressing. This should not be a clinically relevant issue, since these dressings are used AFTER fasciotomy has occurred for presumed or prophylaxis of ACS.

8. No physical modifications to the underlying technology (Task 4) are needed for the prototype development of the INVOS 5100C as a diagnostic device for ACS. Innovations will be needed only in data interpretation algorithms and in the embodiment of the device (i.e. #6 above).

REPORTABLE OUTCOMES

Presentations:

1. Freedman BA, Shuler MS, Owens LE, Lackie DA, Cole AL, Ethington A, Reisman W, Whitesides T. *Does skin pigment affect near-infrared spectroscopy assessment of leg compartment perfusion*? Society of Military Orthopedic Surgeons Annual Meeting, December 13-17, 2010.

2. Freedman BA, Shuler MS, Owens LE, Lackie DA, Cole AL, Ethington A, Reisman W, Whitesides T. *Does skin pigment affect near-infrared spectroscopy assessment of leg compartment perfusion*? American Academy of Orthopedic Surgeons Annual Meeting, February 15-19, 2011.

CONCLUSION:

This continues to be a very ambitious project for LRMC and the forward deployed research team, but at the same time it remains a much needed one. While we faced a significant issue with the originally submitted Phase 2 protocol application, this will be resolved and will become a new milestone in military research, as the first FDA IDE trial to be conducted in combat. We continue to negotiate these hurdles.

As the attached abstract demonstrates, we are already starting to generate reportable information that contributes to our overall grant aims. This completed data collection on control subjects has led to a greater understanding of the normal performance of NIRS values over time, which will be invaluable in establishing *non*-normal NIRS values in order to anticipate and recognize (diagnose) an impending compartment syndrome, the ultimate goal of this research.

This year has produced the first step in reducing missed cases of ACS, as well as unnecessary fasciotomies, among soldiers injured in battle.

REFERENCES

3. Freedman BA, Shuler MS, Owens LE, Lackie DA, Cole AL, Ethington A, Reisman W, Whitesides T. *Does skin pigment affect near-infrared spectroscopy assessment of leg compartment perfusion*? Society of Military Orthopedic Surgeons Annual Meeting, December 2010.

4. Freedman BA, Shuler MS, Owens LE, Lackie DA, Cole AL, Ethington A, Reisman W, Whitesides T. *Does skin pigment affect near-infrared spectroscopy assessment of leg compartment perfusion*? American Academy of Orthopedic Surgeons Annual Meeting, February 2011.

Appendix 1: ACURO approval for animal use study

DEPARTMENT OF THE ARMY
US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
504 SCOTT STREET
FORT DETRICK, MD 21702-5012

REPLY TO
ATTENTION OF

October 29, 2010

Director, Office of Research Protections
Animal Care and Use Review Office

Subject: Review of USAMRMC Proposal Number DR080018, Award Number W81XWH-09-2-0184 entitled, "Near-Infrared Spectroscopy to Reduce the Prophylactic Fasciotomies for the Missed Cases of Acute Compartment Syndrome in Solders Injured in OEF/OIF"

Principal Investigator Brett Freedman
TRUE Research Foundation
San Antonio, TX

Dear MAJ Freedman:

Reference: (a) DOD Directive 3216.1, "The Use of Laboratory Animals in DOD Programs"
(b) US Army Regulation 40-33, "The Care and Use of Laboratory Animals in DOD Programs"
(c) Animal Welfare Regulations (CFR Title 9, Chapter 1, Subchapter A, Parts 1-3)

In accordance with the above references, protocol DR080018 entitled, "Near Infra-Red Spectroscopy to Reduce Prophylactic Fasciotomies for and Missed Cases of Acute Compartment Syndrome in Soldiers Injured in OEF/OIF," IACUC Protocol Number A2010 1-012 is approved by the USAMRMC Animal Care and Use Review Office (ACURO) for the use of swine and will remain so until its modification, expiration or cancellation. This protocol was approved by the University of Georgia IACUC.

When updates or changes occur, documentation of the following actions or events must be forwarded immediately to ACURO:

- IACUC-approved modifications, suspensions, and triennial reviews of the protocol (All amendments or modifications to previously authorized animal studies must be reviewed and approved by the ACURO prior to initiation.)
- USDA annual program/facility inspection reports
- Reports to OLAW involving this protocol regarding

  a. any serious or continuing noncompliance with the PHS Policy;
  b. any serious deviation from the provisions of the Guide for the Care and Use of Laboratory Animals; or
  c. any suspension of this activity by the IACUC

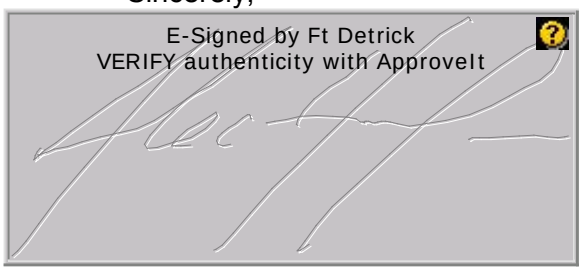
- USDA or OLAW regulatory noncompliance evaluations of the animal facility or program
- AAALAC, International status change (gain or loss of accreditation only)

Throughout the life of the award, the awardee is required to submit animal usage data for inclusion in the DOD Annual Report on Animal Use. Please ensure that the following animal usage information is maintained for submission:

- Species used (must be approved by this office)
- Number of each species used
- USDA Pain Category for all animals used

For further assistance, please contact the Director, Animal Care and Use Review Office at (301) 619-2283, FAX (301) 619-4165, or via e-mail: acuro@amedd.army.mil.

Sincerely,



Alec Hail, DVM, DACLAM
Colonel, US Army
Director, Animal Care and Use
Review Office

Copies Furnished:
Ms. Janet Kuhns, US Army Medical Research Acquisition Activity (USAMRAA)
Dr. Dwayne Taliaferro, Congressionally Directed Medical Research Program (CDMRP)
Dr. Tina Tornambe, University of Georgia
Dr. Christina Heindel, University of Georgia
Dr. Steven C. Budsberg, University of Georgia

 K080769

Section 5 — 510(k) Summary

Date of Submission: ..... March 13, 2008

Device Trade Name: ..... INVOS 5100C Cerebral/Somatic Oximeter System

MAY 14 2008

Device Common Name: ..... Oximeter, Cerebral/Somatic

Device Classification Name: ..... Oximeter, Tissue Saturation (21 CFR 870.2700, Product Code MUD)

Submitted by: .....
Somanetics Corporation
1653 East Maple Road
Troy, MI 48083
Phone: 248-689-3050
Fax: 248-689-4272

Contact Person: .....
Ronald A. Widman
Vice President, Medical Affairs
248-526-5865
rwidman@somanetics.com

Predicate Device: ..... Somanetics INVOS 5100B Cerebral/Somatic Oximeter System, K051274

Device Description: .....

The INVOS 5100C is a 2 wavelength, diffuse reflectance spectroscopy system employing near infrared light to estimate the percentage of hemoglobin saturated with oxygen in tissue underneath the sensor. This is similar to the noninvasive technology widely used in pulse oximeters to monitor oxygen saturated hemoglobin percentage in arterial blood.

An adhesive sensor containing a light source and 2 photodiodes is applied to the skin over the tissue of interest and the returning light is analyzed for hemoglobin and deoxyhemoglobin light absorption. Absorption signals from the photodiode closer to the light source are subtracted from those from the farther photodiode where the returning photons penetrate more deeply in the tissue. This suppresses absorption events originating in the outer layers of tissue that are common to both photodiodes, including the effects of skin pigmentation and subcutaneous tissues.

The INVOS 5100C tissue oximeter is a multi-channel monitor with continuous recording and display of readings of regional tissue hemoglobin oxygen saturation from 4 separate sensors simultaneously. The monitor is connected to 2 preamplifiers, each of which in turn supports 2 sensors. It has USB connectivity for dynamic data capture, storage and transfer as well as a digital output port.

Accessories .....

SAFB-SM	Small Adult SomaSensor (>40 kg)
SPFB	Pediatric SomaSensor (<40 kg)
RSC-1	Reusable Sensor Cable Channel 1
RSC-2	Reusable Sensor Cable Channel 2
RSC-3	Reusable Sensor Cable Channel 3
RSC-4	Reusable Sensor Cable Channel 4
5100C-W	One-year Extension of Warranty
5100C-M	5100C System Operations Manual
4100-FTD	Field Test Device
5100C-RS	Portable Mobile Stand
5100C-SA	Swivel Arm
5100C-GCX	Mounting Plate
5100C-TC	Travel Case
5100C-USB	USB Flash Drive
312170	Computer Connection Serial Cable
VL1	Philips VueLink Adaptor Cable

Indications for Use:.....The noninvasive INVOS 5100C is intended for use as an adjunct trend monitor of regional hemoglobin oxygen saturation of blood in the brain or in other tissue beneath the sensor. It is intended for use in any individual at risk for reduced-flow or no-flow ischemic states.

The prospective clinical value of data from the INVOS System has not been demonstrated in disease states. The INVOS System should not be used as the sole basis for diagnosis or therapy.

Technological Characteristics:.....Technological characteristics of the device, including design, material, chemical composition and energy source are similar to the INVOS 5100B predicate device.

Performance Data: .....Performance data and extensive literature references were submitted demonstrating the substantial equivalence of the device for its stated indication.

Conclusion Drawn from the Testing:.....The conclusion drawn from the testing is the INVOS System can respond with significant changes during isolated desaturation events in kidney and gut tissues. Monitoring the body with the INVOS System can include organ or intestinal oxygenation as well as skeletal muscle tissue oxygen saturation changes depending on the anatomy.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Somanetics Corporation
% Mr. Ronald A. Widman
VP, Medical Affairs
1653 East Maple Road
Troy, Michigan 48083

MAY 14 2008

Re: K080769
Trade/Device Name: Somanetics INVOS® 5100C System and Accessories
Regulation Number: 21 CFR 870.2700
Regulation Name: Oximeter
Regulatory Class: II
Product Code: MUD
Dated: March 13, 2008
Received: March 18, 2008

Dear Mr. Widman:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Center for Devices and Radiological Health's (CDRH's) Office of Compliance at (240) 276-0115. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). For questions regarding postmarket surveillance, please contact CDRH's Office of Surveillance and Biometric's (OSB's) Division of Postmarket Surveillance at (240) 276-3474. For questions regarding the reporting of device adverse events (Medical Device Reporting (MDR)), please contact the Division of Surveillance Systems at (240) 276-3464. You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (240) 276-3150 or at its Internet address http://www.fda.gov/cdrh/industry/support/index.html.

Sincerely yours,

Mark N. Melkerson
Director
Division of General, Restorative
and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

Section 4 **Indications for Use**

510(k) Number (if known) K080769

Device Name: Somanetics INVOS® 5100C System and Accessories

Indications For Use:

The noninvasive INVOS 5100C is intended for use as an adjunct trend monitor of regional hemoglobin oxygen saturation of blood in the brain or in other tissue beneath the sensor. It is intended for use in any individual at risk for reduced-flow or no-flow ischemic states.

The prospective clinical value of data from the INVOS System has not been demonstrated in disease states. The INVOS System should not be used as the sole basis for diagnosis or therapy.

Prescription Use ✓ OR Over-The-Counter Use _____
(Part 21 CFR 801 subpart D) (21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

Neil R. Ogden for mxm

(Division Sign-Off)
Division of General, Restorative, and Neurological Devices

510(k) Number K080769

Posted November 13, 2003

Near-Infrared Spectroscopy in Lower Extremity Trauma

Michael S. Shuler, William M. Reisman, Thomas E. Whitesides, Jr., Tracy L. Kinsey, E. Mark Hammerberg, Maria G. Davila and Thomas J. Moore
J Bone Joint Surg Am. 2009;91:1360-1368. doi:10.2106/JBJS.H.00347

Near-Infrared Spectroscopy in Lower Extremity Trauma

By Michael S. Shuler, MD, William M. Reisman, MD, Thomas E. Whitesides Jr., MD, Tracy L. Kinsey, MSPH, E. Mark Hammerberg, MD, Maria G. Davila, MD, and Thomas J. Moore, MD

Investigation performed at Grady Memorial Hospital and Emory University, Atlanta, Georgia

Background: Near-infrared spectroscopy measures the percentage of hemoglobin oxygen saturation in the microcirculation of tissue up to 3 cm below the skin. The purpose of this study was to describe the measurable response of normal tissue oxygenation in the leg after acute trauma with use of this technique.

Methods: Twenty-six patients with acute unilateral tibial fractures and twenty-five uninjured volunteer control subjects were enrolled. Near-infrared spectroscopy measurements were obtained for both legs in all four compartments: anterior, lateral, deep posterior, and superficial posterior. The twenty-six injured legs were compared with twenty-five uninjured legs (randomly selected) of the volunteer control group, with the contralateral limb in each patient serving as an internal control.

Results: The mean tissue oxygenation for each compartment in the injured legs was 69% (anterior), 70% (lateral), 74% (deep posterior), and 70% (superficial posterior). In the control (uninjured) legs, the average tissue oxygenation percentage in each compartment was 54%, 55%, 60%, and 57%, respectively. Repeated-measures analysis revealed that near-infrared spectroscopy values averaged 15.4 percentage points (95% confidence interval, 12.2 to 18.6 percentage points) higher for injured legs than for uninjured legs, controlling for the value of the contralateral limb ($p < 0.0001$).

Conclusions: Tibial fracture produces a predictable increase in tissue oxygenation as measured by near-infrared spectroscopy. The corresponding compartment of the contralateral leg can provide strong utility as an internal control value when evaluating the hyperemic response to injury.

Level of Evidence: Prognostic Level I. See Instructions to Authors for a complete description of levels of evidence.

The tibia is the most commonly fractured long bone in adults[1]. A potentially devastating complication associated with tibial fractures is the development of compartment syndrome. The prevalence of compartment syndrome has been reported to be as high as 10% in closed tibial fractures[2], and as high as 20% in the intensive care setting[3]. Near-infrared spectroscopy measures the percentage of hemoglobin saturated with oxygen in the microcirculation of tissue within approximately 2 to 3 cm below the skin[4-7]. This technology has been used to examine both acute and chronic compartment syndromes of the lower leg in prior studies[8-12]. However, no data have been published regarding near-infrared spectroscopy values in patients without compartment syndrome.

Near-infrared spectroscopy has been studied, validated, and approved by the U.S. Food and Drug Administration in the anesthesia setting to monitor cerebral oxygenation[4,13]. Light in the near-infrared range (600 to 1000 nm) is capable of penetrating through skin, soft tissue, and bone. The majority of light absorption is based on the relative concentrations of oxygenated and deoxygenated hemoglobin in the microcirculation. Since large vessels or hematomas absorb the light completely, the only light collected by the sensors is light that is capable of passing through the microcirculation[4]. By using the Beer-Lambert law and two separate wavelengths of near-infrared light, the concentration of both oxygenated and deoxygenated hemoglobin can be estimated[14]. The depth of tissue

Disclosure: In support of their research for or preparation of this work, one or more of the authors received, in any one year, outside funding or grants of less than $10,000 from Somanetics. Neither they nor a member of their immediate families received payments or other benefits or a commitment or agreement to provide such benefits from a commercial entity. No commercial entity paid or directed, or agreed to pay or direct, any benefits to any research fund, foundation, division, center, clinical practice, or other charitable or nonprofit organization with which the authors, or a member of their immediate families, are affiliated or associated.

penetration (or the location of tissue oxygenation measurement) is directly proportional to the distance or separation between the light source and the light receptor[5,6].

Cerebral oximetry with use of near-infrared spectroscopy was shown to reflect a weighted average of approximately 3 to 1 of jugular (venous) to carotid (arterial) oxygen saturation[5,15,16]. Since cerebral blood by volume is more venous than arterial, a venous weighted average is consistent with the blood oxygenation as a whole in the brain[17]. When the venous oxygenation status is used to monitor perfusion, the relationship between the oxygen supply and consumption can be monitored. If tissue perfusion does not match oxygen consumption, more oxygen will be extracted from the arterial blood, resulting in lower venous oxygen saturation. Therefore, venous weighted oxygen saturation reflected in near-infrared spectroscopy measurements can be used as a surrogate for tissue perfusion.

Multiple studies have validated cerebral oximetry. The near-infrared spectroscopy responsiveness and changes in jugular oxygen saturation in normal and hypoxic volunteers were shown to be highly correlated[4,5,15-19]. Additional studies have shown minimal effects of subcutaneous blood flow when monitoring cerebral oxygenation during carotid endarterectomy. Only a 2% change in tissue oxygenation was seen when the external carotid artery, the arterial blood supply to the subcutaneous tissue of the forehead, was clamped off during the procedure[15,16,20,21]. Through multiple investigations, near-infrared spectroscopy has been shown to offer a reliable, noninvasive, continual, and real-time means of monitoring tissue oxygenation in the brain and in muscle[18,19,22].

The purpose of this study was to describe the expected alteration of normal tissue oxygenation in the lower leg in the setting of acute trauma without compartment syndrome. Secondarily, the utility of using the contralateral leg as a control measurement was examined. Without knowledge of what happens in trauma patients without compartment syndrome, a deviation from these norms cannot be identified in patients who potentially have a compartment syndrome.

Materials and Methods

The study group consisted of twenty-six consecutive patients with an acute unilateral tibial fracture, and the control group consisted of twenty-five uninjured volunteer subjects. All participants were recruited at a level-I trauma center between February 25, 2007, and July 1, 2007, after approval from the institutional review board.

For the trauma group, the inclusion criteria consisted of unilateral tibial fractures, including proximal intra-articular (plateau), tibial shaft, and distal intra-articular (pilon) fractures as well as open fractures. Exclusion criteria for the injured group included bilateral lower extremity injury, a previous diagnosis of pulmonary or vascular disease, or an inability and/or unwillingness to provide informed consent. Injuries occurring more than sixty hours prior to measurement were excluded since complications associated with acute injury are less likely after this time.

Twenty-six consecutive trauma patients who met the inclusion criteria were studied. No patient who was asked to participate declined to participate. Four patients were excluded from participation on the basis of a possible or verified compartment syndrome at the time of the initial evaluation.

Uninjured control subjects were recruited from the available pool of family members of clinic patients and clinical staff who were willing to volunteer for the study. Exclusion criteria for the uninjured control group included a previous diagnosis of pulmonary or vascular disease, acute injury of any type, or an inability or unwillingness to provide informed consent. Controls were selected to represent a demographically diverse population of healthy nonelderly adults.

For each participant of both the injured and control groups, near-infrared spectroscopy measurements were obtained, with use of the INVOS cerebral oximeter (model 41000; Somanetics, Troy, Michigan) from both the right and left legs at the mid-tibial level for each of the four muscle compartments: anterior, lateral, deep posterior, and superficial posterior. The device consists of a disposable adhesive sensor pad with wires leading to a processor and a display monitor. Near-infrared spectroscopy readings for tissue oxygenation were displayed in the form of a percentage representing the proportion of hemoglobin saturated with oxygen; therefore, a higher reading or percentage is indicative of higher tissue oxygenation. On the basis of the set distance between the light source and the light sensors in the INVOS pad, the depth of tissue monitoring is between 2 and 3 cm deep to the surface of the skin[5]. The INVOS sensor uses two separate measurement depths, and the shallow values are subtracted from the deeper readings in order to isolate the perfusion of the tissue at the deeper level[5].

Readings were obtained by placing the sensor pad over the middle one-third of the tibia for all four compartments. The sensor was applied to the leg for approximately thirty to sixty seconds to obtain a stable reading. The near-infrared spectroscopy device cycles every six seconds to generate a new reading. A stable reading was defined as four consecutive cycles with the same value. A stable reading was obtained within sixty seconds in all legs.

In all injured patients, the tibial fracture was provisionally reduced with traction in order to restore the relative anatomical position. Traction was not applied during the readings in order to minimize any increase in intracompartmental pressure[23,24]. All measurements were made with the heel placed on a rolled towel to remove the pressure caused by the weight of the leg. The foot was maintained in a neutral position. All patients were in a reclined supine position at the time of measurement. Readings were obtained once the patient was hemodynamically stable. Calibration of the device is performed at the time of manufacture and is retained on a microchip in the sensor and monitor. The calibration algorithm is based on the Beer-Lambert law that is modified for spatial resolution (looking at the slope of extinction at progressively deeper penetration depths). Since the blood being measured is a mixture of both oxygenated and deoxygenated blood, the

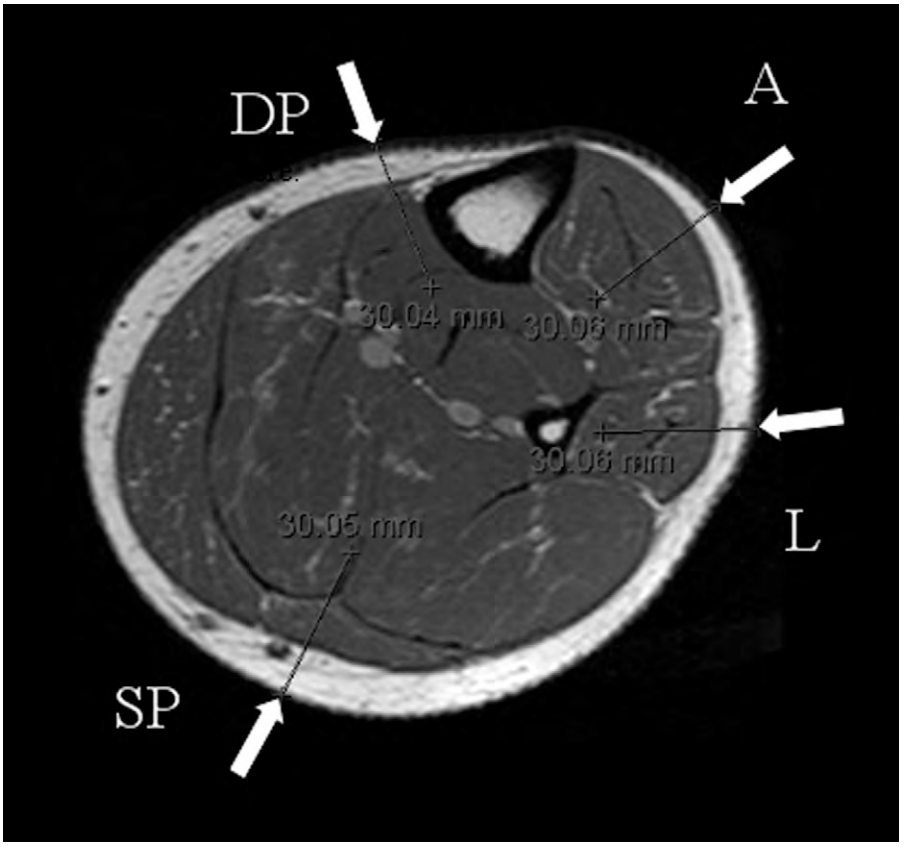


Fig. 1

A T1-weighted axial magnetic resonance image through the mid-tibial level shows the location of the four compartments. Four arrows demonstrate where the measurements were made. The thin line shows the depth of 3 cm. The line is not intended to depict the pathway of the light, which is erratic in nature. By measuring the deep posterior (DP) compartment at this location, a value can be obtained while limiting the amount of superficial posterior (SP) compartment interference. A = anterior, and L = lateral.

values fall between the two extinction curves for deoxygenated hemoglobin (0%) and oxygenated hemoglobin (100%)[5]. The system does not require additional calibration at the time of use[25].

The anterior compartment was accessed by placing the pad lateral to the anterior tibial ridge. The lateral compartment was measured over the anterior aspect of the fibula on the lateral aspect of the leg. The superficial posterior compartment measurement was made by placing the pad on the posterior aspect of the leg. The deep posterior compartment was measured by placing the sensor just posterior to the medial aspect of the tibia over the flexor digitorum longus. The medial aspect of the tibia was palpated until the posterior border was identified, and the pad was placed so that the light would be directed just posterior to the tibia. By placing the sensor at this point, it is possible to obtain a deep posterior measurement, while limiting the potential interference from the superficial posterior compartment (Fig. 1).

The mid-tibial level was selected for measurements in order to compare uninjured and injured subjects. Since no data exist on near-infrared spectroscopy values at different locations in the leg, the goal was to eliminate potential confounding factors by maintaining a consistent location on the leg for measurements. Additionally, the mid-tibial level maximized the muscle cross-sectional area while limiting superficial posterior compartment overlap of the deep compartment.

For a few limbs with a tibial fracture, the technique for obtaining near-infrared spectroscopy measurements required modification. The near-infrared spectroscopy values are not obtainable over hematomas, since the light is completely absorbed by the collection of blood[4]. If a reading at the mid-tibial level was unobtainable, a stable reading was obtained as close to the middle of the leg as possible by moving the sensor either proximally or distally along the axis of the compartment. In the case of open wounds, the skin was manually reapproximated at the time of fracture reduction in the emergency department in order to obtain a reading over intact skin. This process was performed to ensure that any effects of the skin were consistent. All measurements were obtained within the middle one-third of the tibia despite these alterations.

TABLE I Demographic Data for the Injured and Uninjured Groups

	Injured Patients (N = 26)	Uninjured Control Subjects (N = 25)
Age* *(yr)*	36 (18-60)	34 (18-58)
Body mass index*	28.3 (20.4-43.1)	27.0 (20.7-35.8)
Sex (F/M)	5/21	8/17
Race (white/black)	8/18	9/16
Mean blood pressure (systolic/diastolic)	133/72	130/77

*The values are given as the mean, with the range in parentheses.

Statistical Analysis

The analysis was designed to compare the injured legs of twenty-six patients who had an acute tibial fracture and the uninjured legs (randomly selected) of twenty-five control patients, with the contralateral, uninjured leg of each patient used as an internal control for baseline oxygen saturation. The near-infrared spectroscopy values of injured, uninjured, and contralateral (all uninjured) legs were tabulated as means, standard deviations, and ranges. The correlation between alternate legs of uninjured subjects was described with use of the Pearson correlation coefficient. Differences in crude baseline values between black and white subjects were tested with use of the two-sample t test. The effect of trauma on the near-infrared spectroscopy values was evaluated by repeated-measures analysis with use of a generalized linear mixed model, which controlled for the near-infrared spectroscopy value of the contralateral limb. In addition to summarizing the average differences between fractured and uninjured legs across the four compartments, the repeated-measures model allowed us to test directly whether average near-infrared spectroscopy values differed among any of the compartments, as well as whether the amount of difference in near-infrared spectroscopy values associated with the presence compared with the absence of fracture differed among any of the compartments. Because skin pigmentation could affect the near-infrared spectroscopy measurement, race was included as a covariate. Linear regression was used to obtain R^2 values for the prediction of near-infrared spectroscopy values within each compartment individually. The R^2 value represents the proportion of the variance in an outcome variable (i.e., the near-infrared spectroscopy value) that is explained by predictor variables (i.e., fracture status and near-infrared spectroscopy value in the contralateral leg). We used R^2 in this study to quantify the utility of the near-infrared spectroscopy value in the contralateral limb as an internal control. Alpha was set at 0.05 (two-sided) for all statistical tests.

A prestudy power analysis had determined that twenty-four study patients and twenty-four control subjects would provide 80% power to detect a bivariate difference at a two-sided significance level of 0.05 if the true difference between the mean near-infrared spectroscopy values of the injured and uninjured patients was at least 5 percentage points. The analysis assumed a normally distributed response variable with a standard deviation of 6.1 percentage points, which was based on a pilot study of uninjured subjects.

TABLE II Near-Infrared Spectroscopy Results for the Twenty-five Subjects in the Uninjured Group*

	Anterior	Lateral	Deep Posterior	Superficial Posterior
Uninjured (control) leg†				
Mean	54	55	60	57
Median	54	52	60	57
Standard deviation	8.5	8.9	10.4	11
Range	42 to 74	43 to 74	42 to 81	37 to 76
Contralateral leg				
Mean	55	56	59	59
Median	56	53	59	61
Standard deviation	8.1	9.1	10.4	10
Range	42 to 68	42 to 74	43 to 88	40 to 77
Difference between control and contralateral leg				
Mean	−1	−0.3	0.2	−1.9
Median	−2	−1	−1	−3
Standard deviation	4	4.7	5.1	4.7
Range	−8 to 6	−8 to 6	−7 to 12	−9 to 9

*The values are given as the percentage oxygenation. †For the uninjured patients, one leg was randomly selected to be the control leg for comparison with the injured patients.

TABLE III Near-Infrared Spectroscopy Results for the Twenty-six Patients in the Injured Group*

	Anterior	Lateral	Deep Posterior	Superficial Posterior
Injured leg				
Mean	69	70	74	70
Median	70	69	74	71
Standard deviation	7.9	9.4	9.4	9
Range	54 to 82	49 to 90	54 to 90	49 to 87
Contralateral leg				
Mean	55	55	57	57
Median	54	54	57	56
Standard deviation	7.9	9.3	8.1	8.7
Range	44 to 73	43 to 81	43 to 75	43 to 74
Difference between legs†				
Mean	14	15	17	14
Median	12	13	17	13
Standard deviation	7.7	7.7	6.5	6
Range	5 to 34	5 to 37	2 to 28	5 to 28

*The values are given as the percentage oxygenation. †The difference between the injured leg and the contralateral leg for each individual.

Source of Funding
There was no external funding source. However, Somanetics donated the near-infrared spectroscopy equipment for the purpose of the study.

Results

The demographic characteristics of the participants are shown in Table I. For the injured group, the lower extremity trauma consisted of a plateau fracture (four patients), tibial shaft fracture (seventeen patients), or pilon fracture (five patients). There were seven open tibial fractures. One of them was classified as a Gustilo grade I, while three were grade-II and three were grade-IIIA injuries[26,27]. The average time between injury and measurement was 16 ± 12 hours (range, two to fifty-two hours). A motor vehicle accident was responsible for the injury in sixteen patients, while a fall accounted for

TABLE IV Near-Infrared Spectroscopy Values for the Uninjured, Contralateral Limbs According to Race*

	Anterior	Lateral	Deep Posterior	Superficial Posterior
White patients (n = 17)				
Mean	60	62	64	65
Median	62	61	65	66
Standard deviation	8.7	10.7	10.9	9.3
Range	46 to 73	43 to 81	43 to 88	45 to 77
Black patients (n = 34)				
Mean	53	52	55	55
Median	53	52	54	55
Standard deviation	6.2	6.3	6.7	7.6
Range	42 to 65	42 to 68	43 to 76	40 to 75
Difference between white and black patients				
Mean	7.4	9.4	8.9	9.9
95% confidence interval	3.2 to 11.7	4.6 to 14.1	3.8 to 14.0	5.0 to 14.8
P value†	0.0044	0.0031	0.0056	0.0007

*The values are given as the percentage oxygenation. †T tests, assuming unequal variance.

TABLE V Results from the Generalized Linear Mixed Model for the Prediction of Near-Infrared Spectroscopy Values Among the Twenty-six Patients with Unilateral Tibial Fractures and Twenty-five Uninjured Control Subjects

	Parameter Estimates				Tests of Fixed Effects*		
Indicator	Estimate (percentage oxygenation)	Standard Error	95% Confidence Interval	P Value	Degrees of Freedom	F Value	P Value
Intercept†	57.1	1.01	55.1 to 59.2	<0.0001			
Fracture							
Yes	15.4	1.59	12.2 to 18.6	<0.0001	1/48	157.8	<0.0001
No	Referent						
Compartment‡							
Superficial posterior	0.5	0.96	−1.4 to 2.4	0.5966	3/143	6.5	0.0004
Deep posterior	2.6	0.98	0.7 to 4.6	0.0077			
Lateral	0.9	0.54	−0.2 to 1.9	0.1059			
Anterior	Referent						
Compartment × fracture							
Superficial posterior/fracture	−0.6	1.9	−4.3 to 3.2	0.7697	3/143	0.2	0.9253
Deep posterior/fracture	0.4	1.72	−3.0 to 3.8	0.8242			
Lateral/fracture	−0.1	1.43	−2.9 to 2.7	0.9471			
Anterior/fracture	Referent						
Near-infrared spectroscopy value for contralateral leg†	0.67	0.06	0.54 to 0.79	<0.0001	1/143	112.8	<0.0001
Black patients							
Yes	−3.1	1.28	−5.7 to −0.6	0.0173	1/48	6.1	0.0173
No	Referent						

*Type III tests (fully controlled). †Data for the near-infrared spectroscopy values for the contralateral leg were centered on their overall mean value of 56.65 because this produced a more interpretable intercept with a lower standard error. The intercept of this model therefore represents the predicted near-infrared spectroscopy value for the anterior compartment of a nonblack patient without a fracture who has an average value for near-infrared spectroscopy of the contralateral leg. The coefficient for the near-infrared spectroscopy value of the contralateral leg represents the change for each unit value difference in relation to 56.65. ‡Data were unavailable for the deep posterior compartment for three injured patients.

seven injuries and a pedestrian-motor vehicle accident accounted for three injuries. At the time of measurement, all patients were hemodynamically stable with an average blood pressure of 133/72 mm Hg (Table I).

The mean values for the anterior, lateral, deep posterior, and superficial posterior compartments were 69%, 70%, 74%, and 70%, respectively, for the injured legs and 54%, 55%, 60%, and 57% for the uninjured control group (Tables II and III). For the uninjured volunteers, the near-infrared spectroscopy values were highly correlated between the control limbs and the contralateral limbs in all compartments (Pearson product moment correlation, $r = 0.888$, 0.866, 0.879, and 0.905, respectively; $p < 0.0001$ for all). The black patients had substantially lower mean raw near-infrared spectroscopy values than the white patients (Table IV).

The repeated-measures model revealed that near-infrared spectroscopy values were an estimated 15.4 percentage points (95% confidence interval, 12.2 to 18.6 percentage points) higher among the injured legs than among the uninjured legs across the four compartments, controlling for the baseline value of the contralateral leg and race ($p < 0.0001$). The model results are summarized in Table V. The alteration of near-infrared spectroscopy associated with the presence of a fracture did not differ significantly among any of the four compartments ($p = 0.9253$ for effect of compartment × fracture interaction); however, the values themselves were not equal across the four compartments ($p = 0.0004$ for effect of compartment) (Table V). Post hoc contrast tests revealed that the deep posterior compartment differed modestly from each of the other three compartments, while the anterior, lateral, and superficial posterior compartments were not significantly different from one another. The largest of those differences was between the deep posterior and anterior compartments (estimated difference, 2.6 percentage points; 95% confidence interval, 0.7 to 4.6 percentage points). These modest differences of the deep posterior from other compartments are also demonstrated in Tables II and III. The near-infrared spectroscopy value of the contralateral limb was a highly significant covariate ($p < 0.0001$), and the near-infrared spectroscopy values were furthermore lower among blacks

compared with whites in the controlled model ($p = 0.0173$) (Table V).

The presence compared with the absence of a fracture, together with the near-infrared spectroscopy value of the contralateral limb, explained an extremely high proportion (approximately 74% to 80%) of the variance of the near-infrared spectroscopy values that was observed among the fifty-one legs ($R^2 = 0.74$, 0.75, 0.79, and 0.80 for the anterior, lateral, deep posterior, and superficial posterior compartments, respectively), whereas fracture status alone (without the use of the contralateral limb as a control) explained a substantially smaller proportion of only 30% to 47% ($R^2 = 0.47$, 0.41, 0.37, and 0.30 for the respective compartments).

There were no adverse events due to the use of the investigational near-infrared spectroscopy device among any subjects.

Discussion

The body's response to injury is to increase blood flow to the site of trauma. In 1929, Bradburn and Blalock showed a decrease in the arteriovenous oxygen difference in blood from an injured limb[28]. In 1970, Lewis and Lim showed that the increased blood flow after trauma was through capillary beds rather than shunting through larger vessels[29,30]. Imms et al., in 1975, also described a lasting hyperemic effect in soft tissue surrounding a healing fracture of the tibia[31]. In other words, there is a hyperemic response that causes an increase in oxygen saturation in the venous capillary system in response to injury. Since near-infrared spectroscopy measurements reflect a weighted venous arterial average in the capillary bed of soft tissues, the resultant increase in near-infrared spectroscopy values, a measure of microcirculation oxygenation, is consistent with these previous reports[5].

In a study performed on anesthetized dogs, Sandegard and Zachrisson showed with angiograms that vasodilation occurs within thirty seconds in response to trauma in an injured lower extremity[32-34]. There was a decrease in vascular resistance in the injured extremity with a concomitant and inverse increase in resistance in the uninjured leg[32,33]. This response was sustained for several days to weeks after injury[35]. These observations also confirm the hyperemic findings in the injured limbs of this study.

The results from this study show that lower extremity trauma causes a predictable increase in near-infrared spectroscopy values in the absence of compartment syndrome. With all factors considered, a fracture is associated with an average 15.4 percentage point increase in near-infrared spectroscopy values compared with the nonfractured state. This represents an increase of roughly 25% to 30% of baseline values. This hyperemic effect is consistent across all four compartments.

The corresponding compartment of the contralateral leg offered strong utility as an internal control value when evaluating the response to an injury (i.e., the proportion of variation in the near-infrared spectroscopy values explained by our linear regression models increased dramatically with the inclusion of the contralateral limb value—from between 30% and 47% before to between 74% and 80% after the inclusion). The injured extremity showed a hyperemic response in all compartments when the injured extremity was compared with both the uninjured, contralateral side and the uninjured limbs in the study group. The near-infrared spectroscopy values of the tibial compartments appear highly variable among individuals, but they were highly correlated between limbs of the same individual. The uninjured side in the trauma group had mean values (55% to 57%) (Table III) that were similar to those of the uninjured study group (55% to 59%) (Table II), further suggesting that the uninjured side of a trauma patient should be an appropriate control. In our models, it appeared that predictive strength was shared approximately equally by fracture status and near-infrared spectroscopy value of the contralateral limb.

Skin pigmentation does have an effect upon near-infrared spectroscopy values. Black or darker pigmented subjects had attenuated raw near-infrared spectroscopy values, differing by approximately 9 percentage points on the average. The decreased near-infrared spectroscopy values in darker pigmented subjects likely occur because skin pigments absorb more light. This trend is consistent with the finding by Wassenaar and Van den Brand, who examined skin pigmentation in relationship to signal loss in human volunteers with use of a chronic exertional compartment syndrome model[36]. They concluded that melanin played a significant role in the near-infrared spectroscopy signal and light absorption ($p = 0.012$).

Attempts have been made to apply near-infrared spectroscopy in the setting of acute compartment syndrome. An initial animal study showed that near-infrared spectroscopy was inversely related to intracompartmental pressures with use of an infusion compartment syndrome model in pigs[10]. A follow-up study demonstrated the responsiveness of near-infrared spectroscopy in the setting of both hypotension and hypoxemia[8]. In a calf compression model with use of human volunteers, near-infrared spectroscopy was shown to be more sensitive to the ischemic condition measured by nerve conduction studies than when measured by perfusion pressure[37]. Last, in established compartment syndromes, near-infrared spectroscopy values were lower compared with near-infrared spectroscopy values in trauma patients without compartment syndrome[11]. In order to interpret near-infrared spectroscopy values in the trauma setting, normal values for both an uninjured and an injured patient without compartment syndrome must be established.

The results of this study, as well as previous studies, demonstrate that a normal response to soft tissue and osseous trauma is hyperemia and increased perfusion compared with both the uninjured, contralateral leg as well as an uninjured control group. If there is an absence of hyperemia, the clinician should be concerned about impaired oxygenation in the injured leg. The effects of peripheral vascular disease and diabetes are unknown with regard to this response, and additional investigation regarding the effects is required.

These findings have implications when considering the pathophysiology of compartment syndrome. Prior to intracompartmental pressures causing ischemia, these results suggest that there is actually a hyperperfusion period due to a decrease in vascular resistance in response to trauma. In previously described models for compartment syndrome, in which perfusion and intracompartmental pressures were correlated, the response associated with traumatic events has been ignored[8,10,38,39].

There are limitations to this study. As was shown by Heckman et al., the pressure within a compartment can vary on the basis of the distance from the fracture[40]. Since measurements were obtained only at the mid-tibial level, the possibility of different pressures and perfusion along the compartment may not have been appreciated. Additionally, the near-infrared spectroscopy measurements were obtained for only a short period of time, roughly sixty seconds, which limits the information that can be obtained concerning a continuous monitoring system. The hyperemia associated with trauma was consistent despite a wide range of injury patterns and time from injury in this study. Disorders that affect peripheral microcirculation, such as diabetes and peripheral vascular disease, were not examined in this patient cohort. The ability to fully elucidate the effect of skin pigmentation was limited by the sample size and the lack of a quantitative measure of pigmentation. While the deep posterior compartment was measured at the posteromedial border of the tibia, which limits the overlap of the superficial posterior compartment, the proximal half of the tibia typically has some overlap of the superficial posterior compartment. There is evidence to show that the INVOS device does isolate deep-tissue values as it was designed, but there is no so-called gold standard for measurements in the leg[5,16,18,19]. Therefore, the ability of the device to measure the oxygenation of the deep posterior compartment is uncertain.

The findings from this study demonstrate that a predictable hyperemic response occurs in the acute setting of lower extremity trauma. This response is reproducibly detected by near-infrared spectroscopy monitoring. Additionally, the uninjured, contralateral leg appears to provide a highly effective internal control to interpret the findings in the injured leg. Additional studies are required to evaluate the utility of near-infrared spectroscopy in the evaluation of lower extremity trauma and potential compartment syndromes. ■

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Correlation Between Muscle Oxygenation and Compartment Pressures in Acute Compartment Syndrome of the Leg

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Correlation Between Muscle Oxygenation and Compartment Pressures in Acute Compartment Syndrome of the Leg

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Background: Near-infrared spectroscopy estimates soft-tissue oxygenation approximately 2 to 3 cm below the skin. The purpose of the present study was to evaluate muscle oxygenation in the setting of an acute compartment syndrome of the leg and to determine if near-infrared spectroscopy is capable of detecting perfusion deficits.

Methods: Fourteen patients with unilateral lower extremity trauma were enrolled after the diagnosis of an acute compartment syndrome was made clinically and confirmed with intracompartmental pressure measurements. Lower extremity muscle compartments were evaluated with near-infrared spectroscopy, and near-infrared spectroscopy values of the uninjured, contralateral leg of each patient were used as internal reference values. The compartment perfusion gradient was calculated as the diastolic blood pressure minus the intracompartmental pressure.

Results: Intracompartmental pressures ranged from 21 to 176 mm Hg (mean, 79 mm Hg) and exceeded 30 mm Hg in all compartments but two (both in the same patient). Thirty-eight compartments had a perfusion gradient of ≤10 mm Hg (indicating ischemia). Among ischemic compartments, near-infrared spectroscopy values in the anterior, lateral, deep posterior, and superficial posterior compartments of the injured limbs were decreased by an average 10.1%, 10.1%, 9.4%, and 16.3% in comparison with the corresponding compartments of the uninjured leg. Differences in near-infrared spectroscopy values (the near-infrared spectroscopy value for the injured leg minus the near-infrared spectroscopy value for the uninjured leg) were positively correlated with compartment perfusion gradient within each compartment ($r = 0.82$, 0.65, 0.67, and 0.62, for the anterior, lateral, deep posterior, and superficial posterior compartments, respectively; $p < 0.05$ for all).

Conclusions: Normalized near-infrared spectroscopy values decrease significantly with decreasing lower limb perfusion pressures. Near-infrared spectroscopy may be capable of differentiating between injured patients with and without an acute compartment syndrome.

Level of Evidence: Diagnostic Level IV. See Instructions to Authors for a complete description of levels of evidence.

The diagnosis of an acute compartment syndrome is based on clinical suspicion and is confirmed with physical examination and intracompartmental pressure measurements[1,2]. Intracompartmental pressure measurements, the only objective diagnostic tool available to clinicians, are invasive, and values can vary greatly if measurements are not performed correctly[3-8].

Tissue ischemia results from hypoperfusion due to the loss of the pressure gradient between arterial pressure and the intracompartmental pressure. Historically, on the basis of laboratory experimentation in the late 1960s followed by clinical confirmation, Whitesides et al. identified the pressure perfusion gradient at which ischemia is imminent and prophylactic fasciotomy should be done as <20 mm Hg below diastolic blood pressure[2,9,10]. Later, a pressure of 30 mm Hg was suggested as an absolute threshold for the diagnosis of compartment syndrome and was popularized and used for numerous years[11]. However, further research confirmed the importance

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of the pressure gradient between blood pressure and the intracompartmental pressure as a cause of tissue ischemia[1,12-16].

Tissue injury is based on ischemia caused by hypoperfusion or deoxygenation. The measurement of tissue oxygenation has been suggested as a possible noninvasive, continual, and responsive means for physicians to evaluate a suspected compartment syndrome[17-21]. Near-infrared spectroscopy utilizes differential light absorption properties to solve for the concentrations of oxygenated and deoxygenated hemoglobin through the use of the Beer-Lambert law[22-26]. Light in the near-infrared range (600 to 1000 nm) is capable of penetrating through skin, soft tissue, and bone. The majority of light absorption is based on the relative concentrations of oxygenated and deoxygenated hemoglobin in the microcirculation. Because large vessels or hematomas absorb the light completely, the only light collected by the sensors is light that is capable of passing through the microcirculation[25]. This technology is similar to a pulse-oximeter through its use of light to solve for the percentage of oxygenated hemoglobin, but near-infrared spectroscopy is capable of sampling tissue as deep as 3 cm below the skin, such as cerebral tissue and muscle[22,24,27-30]. The depth of tissue penetration or the location of tissue oxygenation measurement is directly proportional to the distance or separation between the light source and the light receptor[22,24].

The purpose of the present study was to evaluate muscle oxygenation of the leg in the setting of acute compartment syndrome with use of near-infrared spectroscopy. We hypothesized that altered (decreased) muscle oxygenation would be correlated with the intracompartmental tissue perfusion gradient and that these responses could be detected with near-infrared spectroscopy.

Materials and Methods

After receiving institutional review board approval and individual patient informed consent, fourteen consecutive patients who were managed for an acute compartment syndrome after unilateral lower extremity trauma were recruited into this study. Treatment was provided at a Level-I trauma center between October 1, 2006, and March 1, 2009.

The study group consisted of consecutive patients with an acute compartment syndrome that had been diagnosed clinically and confirmed with intracompartmental pressure. The cohort consisted of patients between the ages of thirteen and eighty-five years with a unilateral leg injury. Exclusion criteria included bilateral lower extremity injury and previously diagnosed peripheral vascular disease or pulmonary insufficiency. The clinical diagnosis was based on pain out of proportion, pain with passive stretch of the toes and foot, and palpation of firm compartments. Intracompartmental pressure within 30 mm Hg of diastolic blood pressure was used for the confirmation of compartment syndrome and the threshold for surgical release through a four-compartment fasciotomy[4,9,13,14,16,31]. All patients were diagnosed by the senior orthopaedic surgeon at the time of diagnosis prior to recruitment and were determined to require a fasciotomy for treatment.

Once the clinical diagnosis and treatment were determined, the patient was enrolled in the study. Near-infrared spectroscopy values were then recorded prior to intracompartmental pressure measurements to ensure that needle insertion did not influence the near-infrared spectroscopy values. All patients with a clinical diagnosis of acute compartment syndrome had at least one intracompartmental pressure reading within 30 mm Hg of the diastolic blood pressure.

Age, sex, race, body mass index, and blood pressure at the time of evaluation were recorded for each patient. The injury classification, the fracture location, the mechanism of injury, and the time from the injury to measurement were recorded. All measurements, including near-infrared spectroscopy values and intracompartmental pressure measurements, were obtained within one hour after the diagnosis of the compartment syndrome had been determined clinically. Near-infrared spectroscopy and intracompartmental pressure values were obtained after provisional reduction of the fracture in the emergency department. All splints and circumferential bandages were removed prior to measurement. The foot was maintained in a neutral position, with the heel placed on a rolled towel to prevent pressure in the posterior compartments. Intracompartmental pressures were obtained within 5 cm from the fracture[4]. A Stryker pressure gauge (Stryker Surgical, Kalamazoo, Michigan), which employs a side port needle, was utilized to obtain the intracompartmental measurements[3,5,7]. Intracompartmental pressures were obtained in the injured extremity for all four compartments of the leg including the anterior, lateral, deep posterior, and superficial posterior compartments. The compartment perfusion gradient was calculated as the diastolic blood pressure minus the intracompartmental pressure. Near-infrared spectroscopy values were obtained for both the injured side as well as the uninjured side. The data collection methods have been described in previous reports[30].

Near-infrared spectroscopy measurements were obtained as described by Shuler et al.[30]. Briefly, near-infrared spectroscopy measurements were obtained approximately 2 to 3 cm below the skin with use of the INVOS Cerebral Oximeter 4100 (Somanetics, Troy, Michigan). Measurements were obtained at the level of the middle part of the tibia for all four compartments. Near-infrared spectroscopy values represented a percentage of oxygenated hemoglobin and ranged from 25% to 95%. The device is precalibrated during the manufacturing process and does not require additional calibration prior to use[24,30,32].

We distinguished between two types of acute compartment syndrome: clinical compartment syndrome (which constituted a criterion for inclusion in the study) and ischemic compartment syndrome (referring to the presence of a perfusion gradient of ≤10 mm Hg within a compartment). A diagnosis of clinical compartment syndrome was based on physical examination and an intracompartmental pressure within 30 mm Hg of the diastolic pressure as initially described by Whitesides[2,9,33] and confirmed by multiple other authors[14,34,35]. This threshold was advocated in order to perform fasciotomies prior to muscle ischemia, which, when main-

tained for extended periods, results in permanent muscle necrosis. However, altered perfusion has been shown to occur once the intracompartmental pressure nears diastolic pressure[36,37]. Matava et al. showed, in a canine study, that intracompartmental pressure within 20 mm Hg of diastolic pressure resulted in no signs of tissue necrosis whereas intracompartmental pressure held within 10 mm Hg of diastolic pressure resulted in substantial necrosis on pathological examination and loss of contractility on gross examination[13]. This threshold was clinically confirmed by Prayson et al. in a series of patients with isolated lower extremity trauma who were managed nonoperatively without complication[31]. More than half of the patients were shown to have perfusion pressures as low as 20 mm Hg, and more than 80% were found to have perfusion pressures within 30 mm Hg, of diastolic pressure at some point during the evaluation period. Therefore, because near-infrared spectroscopy measures oxygenated hemoglobin concentrations, a change in concentration would not be expected until the intracompartmental pressure was within 10 mm Hg of diastolic pressure[9,13,16,38]. A perfusion pressure of ≤10 mm Hg

TABLE I Intracompartmental Pressures and Near-Infrared Spectroscopy Values Across Compartments for Fourteen Patients with Unilateral Lower Extremity Trauma and Acute Compartment Syndrome With Ischemia* Compared With Literature-Based Values for Comparable Injury Without Acute Compartment Syndrome

	Anterior Compartment	Lateral Compartment	Deep Posterior Compartment†	Superficial Posterior Compartment
Trauma with acute compartment syndrome* *(no. of patients)*	10	11	7	10
Intracompartmental pressure, injured leg *(mm Hg)*				
Mean	99	92	82	82
Standard deviation	35.9	37.7	28.6	20.8
Range*	57 to 170	55 to 176	58 to 135	61 to 115
Near-infrared spectroscopy, injured leg *(%)*				
Mean	45	46	56	49
Standard deviation	14.3	13.4	13.5	14.1
Range	15 to 66	15 to 62	36 to 75	22 to 69
Near-infrared spectroscopy, uninjured leg *(%)*				
Mean	55	56	66	66
Standard deviation	10.8	11.3	7.5	12.0
Range	41 to 76	38 to 76	54 to 75	45 to 85
Near-infrared spectroscopy difference‡ *(%)*				
Mean	–10.1	–10.1	–9.4	–16.3
Standard deviation	11.6	7.4	10.8	15.8
Range	–26 to 8	–25 to 1	–24 to 4	–47 to 3
P value§	0.0001	0.0001	0.0001	0.0003
Trauma without acute compartment syndrome[30] (n = 26)				
Near-infrared spectroscopy difference *(%)*				
Mean	+14.2	+14.9	+17.2	+13.7
Standard deviation	7.7	7.7	6.5	6.0
Range	5 to 34	5 to 37	2 to 28	5 to 28

*Includes compartments with a perfusion gradient (diastolic blood pressure minus intracompartmental pressure) of ≤10 mm Hg (indicating ischemia). †Data were unavailable for the deep posterior compartment of five patients. ‡The near-infrared spectroscopy difference is defined as the near-infrared spectroscopy value for the injured leg minus the near-infrared spectroscopy value for the uninjured leg. §Signed rank test for near-infrared spectroscopy difference between injured and uninjured compartments $\neq 0$.

was considered to be the indication of an ischemic compartment syndrome and was used to differentiate between patients with clinical indications for fasciotomy and those expected to show hypoperfusion.

With regard to outcomes, all patients in the current study received a two-incision four-compartment fasciotomy. There were no signs of muscle necrosis, and all patients had viable tissue at the time of fasciotomy, with the exception of one patient who required débridement of the anterior compartment musculature because of necrosis at the time of fasciotomy. The near-infrared spectroscopy reading over this compartment was 47% and was 29 percentage points below that for the contralateral, uninjured side.

Six postoperative wound complications occurred, including hypergranulation and numbness over split-thickness skin grafts. Three patients required irrigation and débridement because of wound infections, and one of those patients ultimately went on to have a nonunion of the fracture that necessitated revision surgery. One patient required physical therapy to resolve an equinus contracture. An additional patient had a foot drop due to nerve injury associated with the original injuries and ultimately required a rotational flap for wound coverage. Three patients ultimately were lost to follow-up after the immediate postoperative period.

Statistical Analysis

Intracompartmental pressure and near-infrared spectroscopy values were summarized as means, standard deviations, and ranges across compartments. Differences in near-infrared spectroscopy values between the injured and uninjured sides were tested for significance with use of the signed rank test. The perfusion gradient was calculated for each compartment as the difference between the diastolic blood pressure and the intracompartmental pressure. A negative value for the perfusion gradient indicates that the compartment pressure exceeded the diastolic blood pressure. The relationship of the perfusion gradient to the near-infrared spectroscopy difference was characterized with use of graphical methods and Spearman

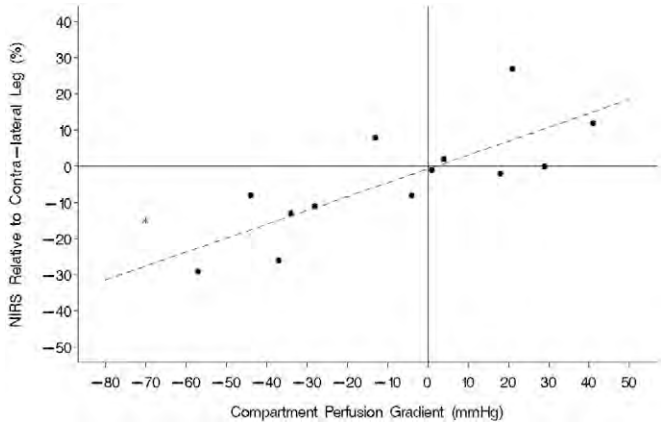

Fig. 1-A

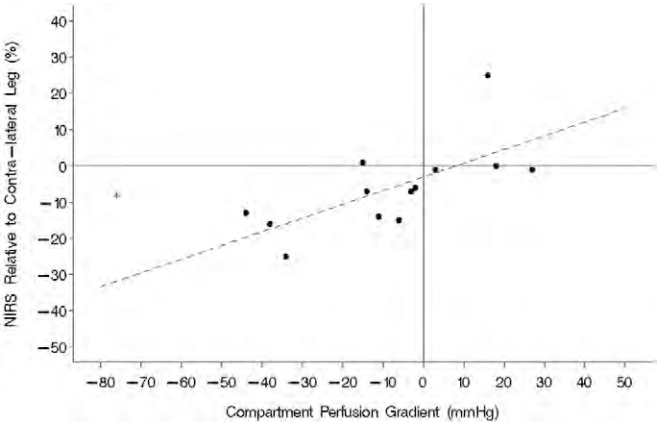

Fig. 1-B

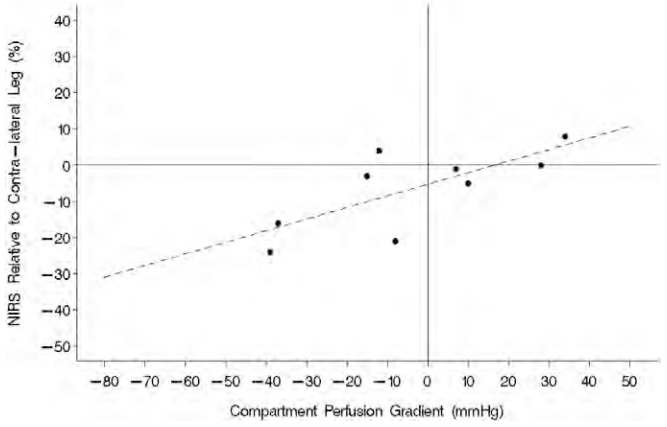

Fig. 1-C

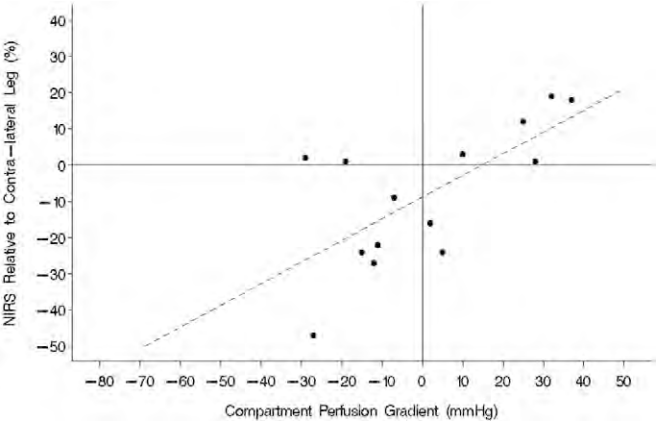

Fig. 1-D

Figs. 1-A through 1-D Scatter plots showing a positive linear correlation between the perfusion gradient (the diastolic blood pressure minus the compartment pressure) and the near-infrared spectroscopy (NIRS) difference (the value for the injured leg minus the value for the uninjured leg) for the four lower extremity muscle compartments. **Fig. 1-A** Anterior compartment ($r = 0.82$, $p = 0.001$). **Fig. 1-B** Lateral compartment ($r = 0.65$, $p = 0.016$). **Fig. 1-C** Deep posterior compartment ($r = 0.67$, $p = 0.049$). **Fig. 1-D** Superficial posterior compartment ($r = 0.62$, $p = 0.018$). The asterisks (*) indicate observations in which the compartment pressure exceeded the systolic blood pressure (see Statistical Analysis).

rank correlation. Because we expected that a linear decrease in near-infrared spectroscopy values with a decreasing perfusion gradient would level off beyond a threshold of very high compartment pressures with absent perfusion, we chose to exclude compartments in which the intracompartmental pressure exceeded the systolic blood pressure from the correlation analysis only. This decision resulted in the exclusion of two measurements in two compartments (in the same patient). These compartments were shown for reference on all scatter plots with use of distinct symbols; however, they were excluded from all correlation statistics and regression calculations.

Nonparametric methods were employed because of the small sample size; symmetric distributions were confirmed graphically. All statistical tests were two-sided, with the level of alpha set at 0.05. A pre-study power analysis indicated that fourteen patients would provide 80% power at an alpha of 0.05 to detect a simple linear correlation between the near-infrared spectroscopy difference and the perfusion gradient within individual compartments, assuming a true population correlation coefficient of r = 0.65[36].

Source of Funding
Funding was provided by Somanetics and Stryker in the form of equipment donation only.

Results

Fourteen male patients with a mean age of 37.4 years (range, fifteen to sixty-two years) were managed for an acute compartment syndrome and participated in the study. Six injuries were on the right side, and eight were on the left. The skeletal injuries consisted of eight tibial shaft fractures (including four in the proximal third of the tibia, three in the middle third, and one in the distal third) and six tibial plateau fractures (including one Schatzker type-III, one Schatzker type-V, and four Schatzker type-VI fractures). The mechanisms of injury included six motor-vehicle accidents, four falls from a height, three pedestrian-automobile accidents, and one gunshot wound. The average time from the injury to measurement was eleven hours (range, five to twenty-eight hours). At the time of evaluation, the mean systolic and diastolic blood pressures were 135 mm Hg (range, 92 to 192 mm Hg) and 72 mm Hg (range, 55 to 100 mm Hg), respectively. Eight patients were black, four were white, one was Hispanic, and one was Asian. The mean body mass index was 26.6 kg/m^2 (range, 22.4 to 31.9 kg/m^2). Five patients were intubated at the time of measurement.

The mean intracompartmental pressure for all compartments of the injured legs was 79 ± 33.0 mm Hg (range, 21 to 176 mm Hg). The intracompartmental pressure was >30 mm Hg in all compartments but two (both in the same patient). Thirty-eight compartments had a perfusion gradient of ≤10 mm Hg (indicating ischemia). Among ischemic compartments, near-infrared spectroscopy values in the anterior, lateral, deep posterior, and superficial posterior compartments of the injured limbs were decreased by an average 10.1%, 10.1%, 9.4%, and 16.3%, respectively, in comparison with the corresponding compartments of the uninjured leg (Table I). Most compartments exhibited near-infrared spectroscopy deficits relative to the uninjured leg (Figs. 1-A through 1-D), and every patient in the present study showed a deficit in at least one compartment. The near-infrared spectroscopy values relative to the uninjured leg (the near-infrared spectroscopy value for the injured leg minus the near-infrared spectroscopy value for the uninjured leg) were positively correlated with the compartment perfusion gradient (the diastolic blood pressure minus the intracompartmental pressure) within each compartment (anterior compartment, r = 0.82, p = 0.001; lateral compartment, r = 0.65, p = 0.016; deep posterior compartment, r = 0.67, p = 0.049; and superficial posterior compartment, r = 0.62, p = 0.018) (Figs. 1-A through 2).

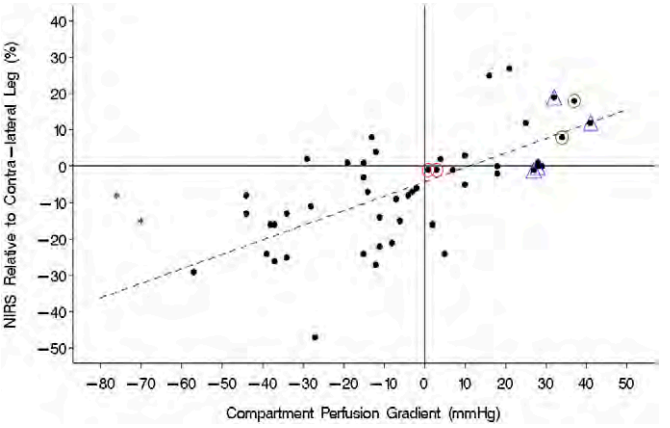

Fig. 2
Scatter plot of pooled compartments, illustrating a linear correlation between the perfusion gradient and the near-infrared spectroscopy (NIRS) difference. Compartments of two selected patients are highlighted to illustrate how the same patient has different compartments with hyperemia and hypoperfusion. The asterisks (*) indicate observations in which the compartment pressure exceeded the systolic blood pressure (see Statistical Analysis).

The first five patients who were enrolled did not have near-infrared spectroscopy measurements for the deep posterior compartment because we had not devised a way to perform the measurements for that compartment until before the sixth patient was enrolled.

Discussion

The body's response to injury is to increase blood flow to the site of trauma[12,39-42]. Near-infrared spectroscopy measurements reflect a weighted venous arterial average in the capillary bed of soft tissues. Sandegård and Lewis studied vasodilation and hyperemia associated with trauma and injury[40,41,43-48]. The finding of increased near-infrared spectroscopy values in the setting of trauma is consistent with these previous reports and was confirmed in previous studies of injured patients without an acute compartment syndrome[24,30].

Near-infrared spectroscopy has previously been utilized in the setting of acute compartment syndrome (although with use of a different device than the one used in the present

study). An initial animal study involving an infusion compartment syndrome model in pigs showed that near-infrared spectroscopy values were inversely related to intracompartmental pressures[18]. A follow-up study demonstrated the responsiveness of near-infrared spectroscopy in the setting of both hypotension and hypoxemia[17]. In a simulated model involving human volunteers, near-infrared spectroscopy was shown to be more sensitive to an ischemic condition measured with nerve conduction studies when compared with perfusion pressure[19]. Last, in a study of patients with an established acute compartment syndrome, near-infrared spectroscopy values were decreased at the time of initial measurement and rebounded after fasciotomy[20].

While the technology of near-infrared spectroscopy has been available for almost two decades, its application for the diagnosis of acute compartment syndrome has been impeded by many factors. First, a publicly available device that provides measurements deep enough to sample leg tissue has not been readily available until recently. Previous near-infrared spectroscopy devices required timely calibration through the induction of ischemia and reperfusion in order to establish 0% and 100% saturation levels. Early devices utilized a single depth of penetration to sample hemoglobin saturation. Newer near-infrared spectroscopy devices utilize multiple levels of sampling to isolate deeper tissue values. In addition, the ability to access the deep posterior compartment was not appreciated prior to the recent description by Shuler et al.[30]. The lack of measurements for the deep posterior compartment in the first five patients was due to the fact that we had not determined this possibility until before the sixth patient was enrolled. Last, the lack of consideration for the hyperemic response to trauma resulted in an underappreciation of the ability of near-infrared spectroscopy to reflect perfusion changes[30].

In order to interpret near-infrared spectroscopy values in the setting of an acute compartment syndrome, normal values for both an uninjured patient and an injured patient without compartment syndrome must be established. It has been shown that lower extremity trauma causes a predictable increase in near-infrared spectroscopy values in the absence of compartment syndrome and that the corresponding compartment of the contralateral leg offers an excellent internal reference value for near-infrared spectroscopy when evaluating the hyperemic response to injury[30]. Shuler et al. demonstrated that lower extremity trauma resulted in an average 15 percentage point increase in near-infrared spectroscopy values (hyperemia) across compartments among twenty-six patients with unilateral injuries who never had development of a compartment syndrome and that the near-infrared spectroscopy values of the injured limb were greater than those of the uninjured limb in every compartment of every patient (minimum difference, +2%)[30].

In contrast, most compartments of our comparably injured patients with an acute compartment syndrome exhibited a deficit in near-infrared spectroscopy values when compared with the values for the contralateral, uninjured leg, with normalized near-infrared spectroscopy values decreasing significantly in proportion to compartment perfusion gradients (Figs. 1-A through 2). These results suggest that if there is an absence of hyperemia in a patient with lower extremity trauma or fracture, the clinician should be concerned about impaired blood flow in the injured leg. Lack of hyperperfusion may be a sign of vascular injury or compartment syndrome. These findings have implications when considering the pathophysiology of compartment syndrome. It has been shown that a hyperemic response follows lower extremity trauma among patients who do not have development of compartment syndrome; accordingly, it seems that the natural course of posttraumatic acute compartment syndrome includes an initial phase of hyperemia prior to the increase of intracompartmental pressure sufficient to induce impaired perfusion.

Notably, there were two patients in the present study who demonstrated both hyperemia and hypoperfusion at the same time. While limited conclusions can be drawn from just two examples, some insight can be obtained from these patients. The first patient had perfusion pressures of 1 and 3 mm Hg in the anterior and lateral compartments, respectively, compared with perfusion pressures of 37 and 34 mm Hg in the superficial and deep posterior compartments, respectively. The compartments consistent with acute compartment syndrome (the anterior and lateral compartments) had a −1% near-infrared spectroscopy value in comparison with the uninjured leg, whereas the superficial and deep posterior compartments had values of +18% and +8%, respectively, when compared with their contralateral counterparts. This patient demonstrated hyperemia in compartments with adequate perfusion pressure (>20 mm Hg) while also showing an absence of hyperemia in compartments with poor perfusion (<10 mm Hg). In addition, the findings for this patient demonstrate how near-infrared spectroscopy is able to differentiate between individual compartments with different perfusion characteristics in the same leg.

The second patient had two compartments with perfusion pressures of >30 mm Hg and two compartments with pressures between 20 and 30 mm Hg. Near-infrared spectroscopy values were elevated in the two adequately perfused compartments demonstrating hyperperfusion. The two compartments with borderline perfusion with gradients between 20 and 30 mm Hg did not show hyperemia and the near-infrared spectroscopy values were roughly equal to those for the uninjured side. The findings for this patient with a borderline acute compartment syndrome suggest that compartment perfusion transitions from hyperemia to hypoperfusion as perfusion pressure drops from 30 to 10 mm Hg, consistent with previous studies[2,13,14,16,38]. These longitudinal trends have not been directly documented, however, and our cross-sectional study design did not afford us the opportunity to observe the pre-ischemic condition of all of the patients. This conjecture warrants further study.

The hyperemia associated with trauma may account for some of the inconsistencies in the literature surrounding acute compartment syndrome. In previously described models

of compartment syndrome in which perfusion and intracompartmental pressures have been correlated, a hyperemic response associated with traumatic events has not been considered[13,17,18,36,37]. In order to adequately reproduce the compartment syndrome model, the traumatic influences and associated hyperemic response must be understood and accounted for when analyzing the pressure and perfusion relationship.

White et al. reported no difference in clinical outcomes between patients with intramuscular pressures above and below the absolute 30-mm-Hg threshold[49]. McQueen and Court-Brown showed that asymptomatic patients had intracompartmental pressures of as high as 50 mm Hg without development of a compartment syndrome[14]. In a study of patients without compartment syndrome who were managed without fasciotomy, Prayson et al. reported perfusion pressures of <20 mm Hg in >50% of the enrolled patients[31]. The existence of hyperemia in response to trauma may play a protective effect in patients with low to moderate intracompartmental pressures and may explain some of the disconnect found between model studies (lack of hyperemia) and clinical studies (presence of hyperemia). Of note, the only study to investigate the possible effects of traumatized tissue on perfusion was that by Heppenstall et al., who hypothesized that the ability of traumatized tissue to tolerate elevated intracompartmental pressures was actually decreased[12].

The present study had limitations. Because measurements were obtained at standardized locations, the possibility of different pressures and variable perfusion along the compartment may not have been appreciated[4]. In addition, the near-infrared spectroscopy measurements were obtained for only a short period of time, roughly sixty seconds, which limits the information that can be obtained concerning a continual monitoring system. Although the patients in the present study were racially varied, our sample size was too small to evaluate or account for the potential influence of variable skin pigmentation on any correlation between near-infrared spectroscopy values and intracompartmental perfusion pressures. In addition, while no attempts were made to exclude female patients, previous studies have shown no difference in the response to trauma between the sexes[30]. In the first five patients, a reading for the deep posterior compartment was not obtained. Because an isolated deep posterior compartment syndrome was not encountered in the present study, it is difficult to determine with certainty the ability of the device to isolate the deep posterior compartment.

The present study was designed to determine the potential for near-infrared spectroscopy to detect decreased perfusion in the setting of an acute compartment syndrome. While the pooled data suggest that the point at which the near-infrared spectroscopy values for both legs become equal is consistent with roughly 10 mm Hg of perfusion pressure, the definition of a critical point was outside of the scope of the present study. Additional studies examining the relationship of intracompartmental pressure and near-infrared spectroscopy values in a continual fashion are indicated. The present study examined near-infrared spectroscopy in patients with an existing compartment syndrome. The next studies should incorporate continual readings for patients as they progress through the development of an acute compartment syndrome in order to identify a critical threshold. This task should be performed through animal and human models as well as blinded observational studies of injured patients. The value of the near-infrared spectroscopy technology is its ability to monitor perfusion over extended periods and to respond in real time. ■

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Appendix 4: 2011 AAOS/2010 SOMOS Accepted Abstract

Do skin pigment and hair affect near-infrared spectroscopy assessment of leg compartment perfusion?

Authors: Freedman BA, Shuler MS, Owens LE, Lackie DA, Cole AL, Ethington A, Reisman W, Whitesides T.

Summary: Early clinical results show near infrared spectroscopy (NIRS) can be an important tool for diagnosing acute compartment syndrome (ACS). This study shows that NIRS values may be affected by skin pigmentation. NIRS values are very reproducible over time at multiple body sites.

Introduction: ACS is a clinical diagnosis, with poor inter/intra-rater reliability. Currently, patients with ACS are being missed, and patients without ACS are being unnecessarily fasciotomized. This study is part of a multi-phased DoD research project, seeking to validate a continuous, noninvasive NIRS ACS monitor for military-use. The purpose of this study is to evaluate the impact of skin pigment and hair on NIRS values in normal controls.

Methods: Forty-one healthy volunteers (14 M; 27 F) were monitored for two 1-hour continuous sessions separated by 1 day, using a standardized protocol, which placed NIRS leads over the 4 compartments of each leg, recording NIRS values (% saturation) every 30sec. Additionally, the dorsal and volar forearm compartments and deltoid were monitored. Colorimeter readings of skin pigmentation from two probes were used to document skin pigmentation. The NIRS values for each compartment were then compared to NIRS readings from corresponding compartments and colorimeter values.

Results: NIRS values in left and right leg are highly conserved. The data is very reproducible with an insignificant (<1%) average difference between day 1 and 2. Upper extremity NIRS values were strongly correlated to leg values in the following order volar (r=.71), dorsal (r=.57) and deltoid (r=.41). A moderate negative correlation was observed between melanin and NIRS values, while "L" values were positively correlated. Shaving did not affect NIRS values.

Conclusions: This study confirms that the contralateral uninjured leg or, in patients with bilateral leg injuries, the volar forearm, are the ideal control sites to compare to the traumatized leg. These data suggest that NIRS values may be affected by a patient's skin pigmentation. However, shaving the leg hair of male patients does not appear to affect NIRS values.

Appendix 5: Selected results from Phase 1 Cohort 1 Analyses

Table 1. Within-patient summary statistics of NIRS values collected over a 1-hour monitoring period from 44 uninjured subjects					
Compartment Mean	Min	Max	SD	Range	
Anterior	72.2 65.5		80.9	2.9	15.3
min-max 48.2-9	1.7	41.0-85.0	55.0-95.0	1.2-6.3	5.0-51.0
Lateral	75.4 70.2		81.3	2.3	11.1
min-max 49.5-9	3.5	45.0-87.0	54.0-95.0	0.5-5.2	2.0-27.0
Superficial Posterior	78.9 73.9		84.1	2.2	10.3
min-max 55.4-9	4.7	53.0-92.0	60.0-95.0	0.8-6.3	3.0-32.0
Deep Posterior	81.8 76.6		86.1	2.1	9.6
min-max 61.7-9	5.0	53.0-95.0	64.0-95.0	0.0-6.7	0.0-26.0
Volar	78.1 70.1		84.6	2.9	14.6
min-max 55.2-9	4.3	15.0-85.0	64.0-95.0	1.0-14.7	5-65
Dorsal	68.9 62.8		78.1	2.8	15.2
min-max 37.8-8	5.8	33.0-78.0	44.0-91.0	1.1-5.7	5.0-34.0
Deltoid	81.8 77.3		85.4	1.6	8.1
min-max 58.9-9	4.4	28.0-92.0	70.0-95.0	0.6-7.3	3.0-46.0

*all values are presented as percent oxygenation

Table 2. Mean difference in NIRS values on Day 1 versus Day 2 for 44 healthy volunteers*								
	Lower Extremity							
	Anterior		**Lateral**		**SP**		**DP**	
Day 1 vs Day 2 (n=44)	Day 1	Day 2	Day 1	Day 2	Day 1	Day 2	Day 1	Day 2
Mean:	73.8	75.0	76.1	76.7	79.1	80.2	83.4	83.6
Mean Difference:	1.2		0.6		1.1		0.2	

*for patients who were shaved on Day 1 (n=10), post-shave data was used

Appendix 5 (continued):

Table 3. Intraclass correlation (ICC) coefficients for reliability of NIRS values from Day 1 and Day 2, among 44 uninjured subjects	
Compartment	ICC
Anterior	0.80
Lateral	0.72
Superficial Posterior	0.81
Deep Posterior	0.70

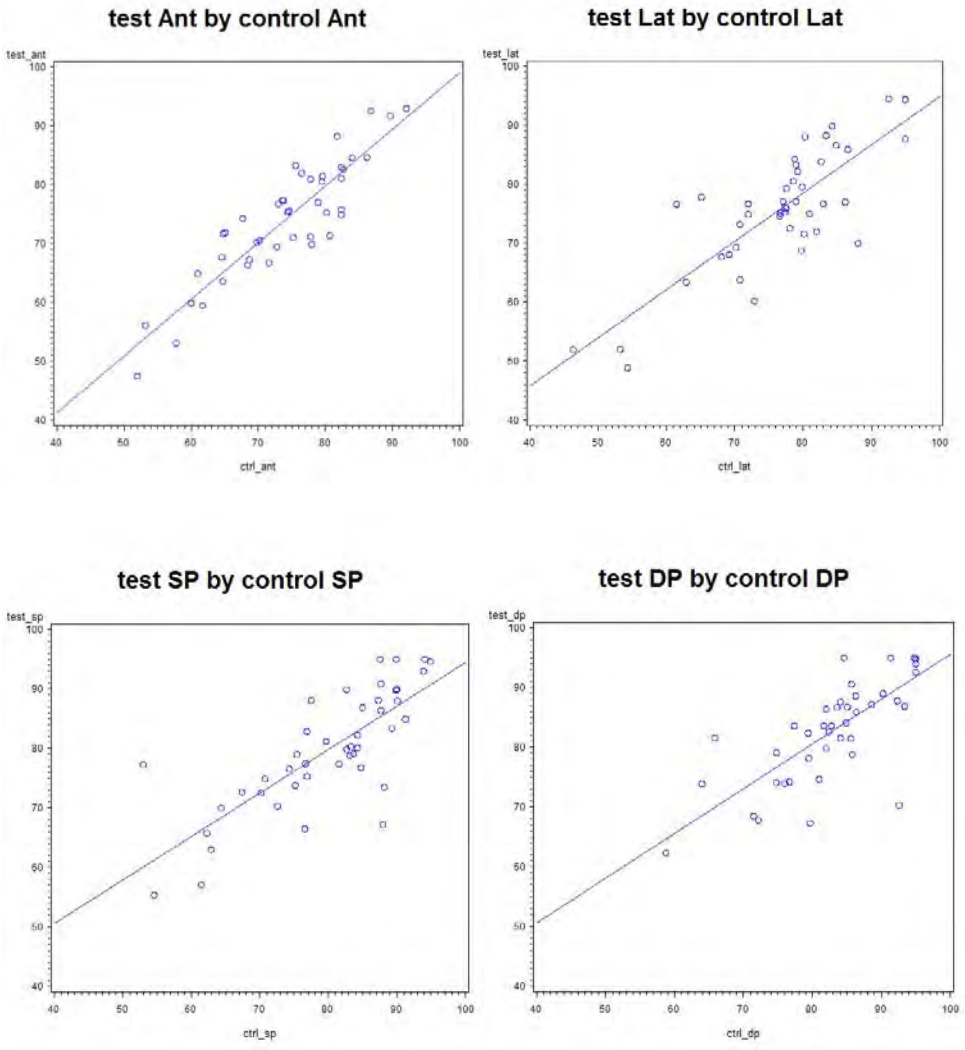
*interpretation of ICC: amount of between-subject variation relative to total variation (including repeatability across days and random variation)

Table 4. NIRS values from each muscle compartment of the lower extremity of 12 uninjured volunteers, taken pre- and post-shave

	Anterior		**Lateral**		**Sup Post**		**Deep Post**	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Mean	67.6	66.8	67.0	71.5	74.8	72.3	76.9	78.2
Min-Max	53.1-83.3	57.0-79.9	51.9-89.9	56.0-86.9	57.1-95.0	55.3-92.6	62.3-95.0	57.2-94.3
Difference*	-0.73		2.54		-2.52		1.28	

Appendix 5 (continued):

Figure 1. Relationship between NIRS values of each muscle compartment of test (randomly-selected) and control lower extremities of 44 uninjured subjects



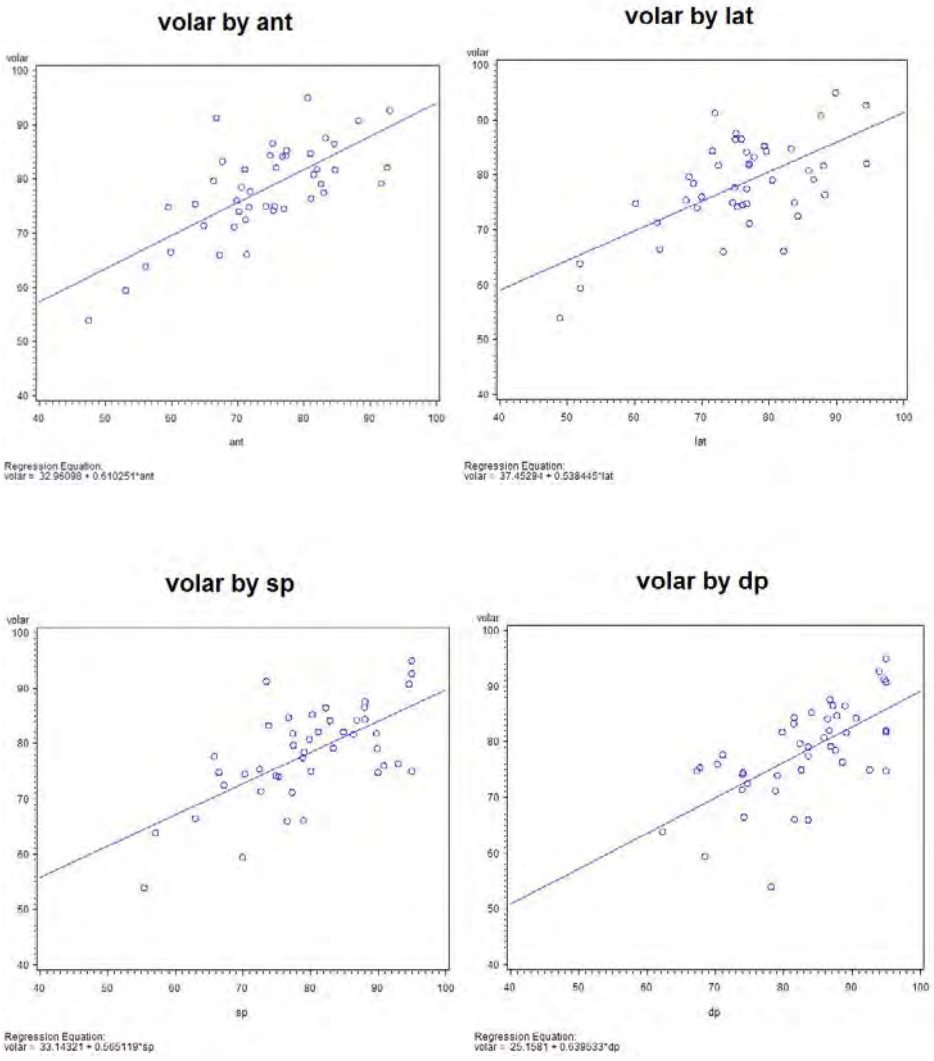
Appendix 5 (continued):

Table 5. Pearson correlation coefficients of NIRS values taken from the upper and lower extremities of 44 uninjured subjects

	Anterior	Lateral	Superficial Posterior	Deep Posterior
Volar	r = 0.71 p<0.0001	r = 0.65 p<0.0001	r = 0.65 p<0.0001	r = 0.65 p<0.0001
Dorsal	r = 0.60 p<0.0001	r = 0.55 p=0.0001	r = 0.55 p=0.0001	r = 0.36 p = 0.02
Deltoid	r = 0.51 p=0.0005	r = 0.50 p=0.0005	r = 0.45 p=0.002	r = 0.42 p=0.005

Appendix 5 (continued):

Figure 2. Relationship between NIRS values of the volar compartment of the upper extremity with muscle compartments of the lower extremity, among 44 uninjured subjects



Freedman, Brett A MAJ MIL USA MEDCOM LRMC

From: Eckart, Robert E LTC USA JC2RT [robert.e.eckart@afghan.swa.army.mil]
Sent: Monday, November 29, 2010 12:22 PM
To: undisclosed-recipients
Cc: Osborne, Lisa A CDR USA USN TF MED SOUTH (JC2RT); Kline, Andrea J Ms CIV USA MEDCOM USAMRMC; Brosch, Laura R Dr CIV USA MEDCOM USAMRMC
Subject: FDA and IDE update from JC2RT (UNCLASSIFIED)

Classification: UNCLASSIFIED
Caveats: FOUO

Principal Investigators,

At the recent CENTCOM Surgeon General briefing in Qatar, the Joint Combat Casualty Research Team led discussion on the challenges in the performance of medical device research in theater. It was emphasized that this was due to regulatory guidance from the FDA and inability to safely obtain written informed consent from trauma casualties. It was a lively discussion, but ultimately, there was definitive agreement - quality research needs to occur for the purpose of optimizing battlefield health.

Ideally, we would like to see a situation where there is waiver of informed consent for those devices with a non-significant risk determination, and in which the study proposed is of no greater than minimal risk.

The attendees included representatives from each of the Service's Office of The Surgeon General and regional command Surgeons.

The decision was made to advance this issue to the Army SG and CG, MRMC at this time.

We thank all of you for your support as we work toward a more definitive solution in the reduction of barriers to research, while optimizing the safety of our servicemembers.

-Rob

ROBERT E. ECKART, LTC MC, FS
Director, USCENTCOM JC2RT
Bagram, Afghanistan
DSN 318-431-9162

Do the right thing, because it's the right thing to do.

Classification: UNCLASSIFIED
Caveats: FOUO

Appendix 7. 2010 SOMOS Poster

Do Skin Pigmentation and Hair Affect Near-Infrared Spectroscopy Assessment of Leg Compartment Syndrome

MAJ Brett Freedman, MD; CPT Keith Jackson, MD; Dwight David Eisenhower Army Medical Center, Ft Gordon, Georgia

Summary

Early clinical results show near infrared spectroscopy (NIRS) can be an important tool for diagnosing acute compartment syndrome (ACS). This study shows that for lower extremity trauma NIRS values from the contralateral leg are highly conserved while the volar forearm is the best comparative site in the upper extremity.

Introduction

•Near-Infrared Spectroscopy (NIRS) is a new technology used to detect the oxygen saturation of hemoglobin in the microcirculation through differences in light absorption.

•Previous investigations have shown that in cases of lower extremity trauma NIRS technology is capable of detecting the increased tissue oxygenation predicted in the normal physiologic state and the ischemic changes expected in cases of compartment syndrome. (1,2)

•In each of these studies the four compartments of the contralateral leg was used as an internal control for the injured extremity.

•The purpose of this study was to validate the contralateral lower extremity as an internal control in cases of unilateral trauma, to validate upper extremity sites as controls in cases of bilateral lower extremity trauma and to determine the effect skin pigmentation and the presence of body hair have on NIRS device readings.

Materials & Methods

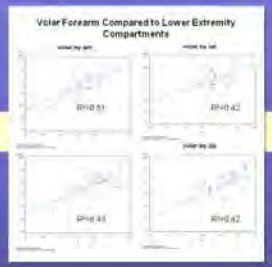
•A prospective study of 44 healthy, uninjured adult volunteers with varying amounts of skin pigmentation and body hair was conducted

•Skin pigmentation was quantified using both the Dermaspectrometer (Cyberderm, Broomall, PA) and Smart Probe 400 (IMS, Inc, Portland, ME) colorimeters.

•Near-Infrared Spectroscopy leads from the INVOS system (Somanetics, Troy, MI) were placed over the 4 compartments of each leg as well as in the upper extremity over the volar forearm, mobile wad and deltoid muscle and values were recorded every 30 seconds for two 1-hour sessions

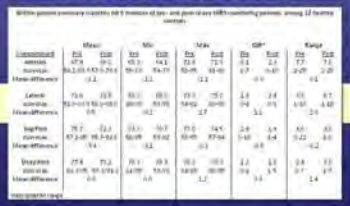
•At the first visit the leads were placed over the individual's native body hair. On the follow-up visit, sites were shaved prior to lead application.

Results



Colorimeter values

Pre vs Post Shave Variability



Discussion

•The results of this study show the contralateral lower extremity is the most accurate comparative site.

•The volar forearm is the most accurate control site in the upper extremity.

•The presence of body hair did not significantly effect NIRS readings in this study.

•A moderate negative correlation exists between the presence of melanin and NIRS values while a positive correlation exists with "L" values and NIRS recordings.

Conclusions

•Near-Infrared Spectroscopy is a promising advance in the development of more accurate, less invasive methods to detect compartment syndrome.

•In cases of unilateral lower extremity trauma the contralateral leg should be used as a comparative control.

•In cases of bilateral lower extremity trauma the volar forearm is the most accurate upper extremity control.

Annotations

1. Shuler MS, Reisman WM, Kinsey TL, et al. Correlation Between Muscle Oxygenation and Compartment Pressures in Acute Compartment Syndrome of the Leg. *J. Bone Joint Surg.* Am Apr 2010;92:863-870.

2. Shuler MS, Reisman WM, Whitesides TE, et al. Near-Infrared Spectroscopy in Lower Extremity Trauma. *J. Bone Joint Surg* Am Jun 2009;91:1360-1368.

Appendix 8: IACUC approval for animal use studies

The University of Georgia
Office of The Vice President for Research

Animal Care and Use
608A Boyd Graduate Studies Building
Athens, Georgia 30602-7411
(706) 542-5933
Fax No. (706) 542-5638

Date: **April 14, 2010**

To : **BUDSBERG, STEVEN C**

From : **Tina Tornambe, IACUC Coordinator**

Regarding : **Initial Approval of Animal Use Protocol**

AUP Approval Date : **4/14/2010 10:45:25 AM**

Title : **Near Infra-Red Spectroscopy to Reduce Prophylactic Fasciotomies for and Missed Cases of Acute Compartment Syndrome in Soldiers Injured in OEF/OIF**

AUP # **A2010 1-012**
Highest Use Category : **Category B**

Source of Support: U.S. Department of Defense
UGA Animal Welfare Assurance # A3437-01

In accordance with the procedures of The University of Georgia Institutional Animal Care and Use Committee (IACUC), your proposal involving the use of animals was approved.

If your funding agency requires notification of animal use approval, please forward a copy of this approval letter to them.

Please let us know if there are any anticipated changes in the use of animals for this proposal. Any significant changes in animal use methodology or numbers of animals must be reviewed by the Committee before implementation.